National Toxicology Program

U.S. Department of Health and Human Services

Annual Report for Fiscal Year 2013

National Toxicology Program

ANNUAL REPORT
for
Fiscal Year 2013

National Institute of Environmental Health Sciences
National Institutes of Health

National Center for Toxicological Research
U.S. Food and Drug Administration

National Institute for Occupational Safety and Health
Centers for Disease Control and Prevention

July 2014

U.S. Department of Health and Human Services

National Toxicology Program

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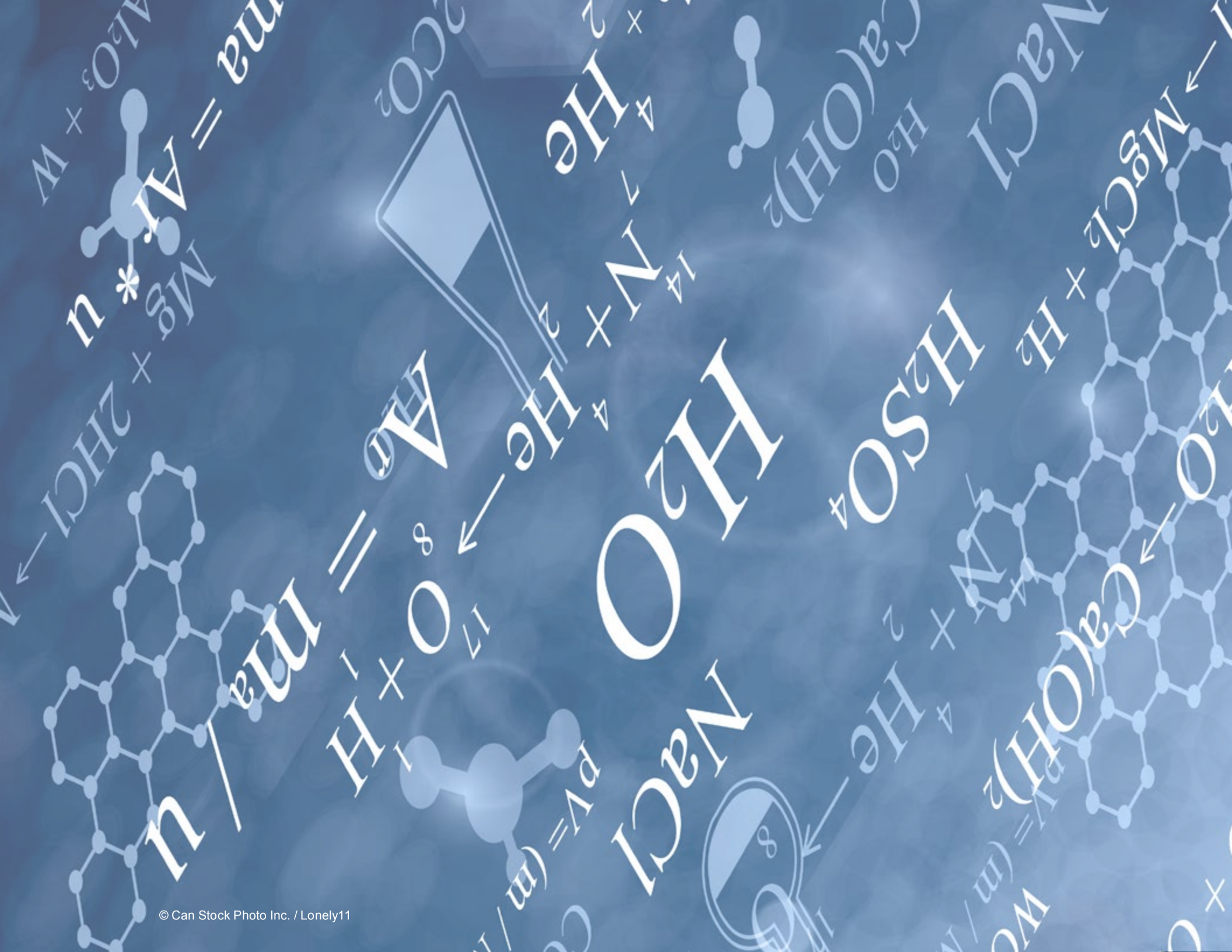

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Letter from the NIEHS and NTP Director

The National Toxicology Program (NTP) made great strides in conducting and coordinating toxicology testing and research, despite facing challenges like the budget sequestration in 2013. With its partners in the federal government, NTP continued to lead the Tox21 initiative to develop more efficient approaches to predict how chemicals may affect human health. NTP also distributed numerous reports on substances of public health concern.

NTP published a monograph on chemotherapeutics use during pregnancy, to serve as a resource for clinicians and their pregnant patients. Through five NTP Technical Reports, we disseminated information from studies on the carcinogenic activity and toxicity of botanical dietary supplements, an antiviral drug, and two substances used in industry. In addition, NTP hosted an international workshop, and published three reports to facilitate the development, validation, and regulatory acceptance of test methods that reduce, refine, or replace the use of animals in testing.

Through fiscal year (FY) 2013, the NTP Office of Health Assessment and Translation widely presented, to agency partners and the public, their draft approach for systematic review and evidence integration for literature-based health assessments. This draft approach describes how NTP will incorporate systematic review methodologies in conducting literature-based analysis of published studies, to assess if a substance may be of concern for human health. This new approach will increase transparency in how NTP conducts and communicates literature-based assessments.

NTP continues to safeguard public health, by strengthening environmental health sciences, and working with partners in the United States and abroad, to improve toxicology research and testing. I am proud to present our achievements in FY 2013.

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S.

1. National Toxicology Program: Mission and Goals

Safeguarding public health depends upon identifying the effects of substances that are in contact with people and their environment, and determining the levels of exposure at which they may become potentially hazardous. The Toxic Substances Control Act Chemical Substance Inventory of January 2013 (*http://www.epa.gov/oppt/existingchemicals/pubs/tscainventory/basic.html*) lists more than 83,000 chemicals as being available for sale and use in the United States. New chemicals are continuously introduced into the U.S. market each year. According to the Board of Governors of the Federal Reserve System, chemical production in the United States increased 2.1-fold from 1972 to 2012 (*http://www.federalreserve.gov/datadownload/default.htm*). While the effects of many of these substances on human health are unknown, people and our environment may be exposed to them during their manufacture, distribution, use, and disposal, or as pollutants in our air, water, and soil.

NTP MISSION:

TO EVALUATE AGENTS OF PUBLIC HEALTH CONCERN BY DEVELOPING AND APPLYING THE TOOLS OF MODERN TOXICOLOGY AND MOLECULAR BIOLOGY

The U.S. Department of Health, Education, and Welfare (now the U.S. Department of Health and Human Services, HHS) established NTP in 1978, as a focal point to coordinate toxicology testing in the federal government. In carrying out its mission, NTP has several goals:

- Coordinate toxicology testing programs within the federal government.
- Strengthen the science base in toxicology.
- Develop and validate improved testing methods.
- Provide information about potentially toxic chemicals to health, regulatory, and research agencies, scientific and medical communities, and the public.

To protect public health, regulatory agencies make decisions based on scientific information. NTP plays a critical role in providing scientific data, interpretation, and guidance in the appropriate uses of these data to regulatory agencies and other health-related research groups. The American people and government agencies, at state and federal levels, rely on NTP to provide a strong scientific basis for making credible decisions that will protect public health.

In following government-wide efforts to increase access to the results of federally funded scientific research, NTP maintains open communications and dialogue with federal and state agencies, industry, nongovernment groups, academia, and the public. The NTP website (*http://ntp.niehs.nih.gov*) provides the public with a variety of information, including Federal Register notices, status and data of NTP studies, lists of reports and journal publications, media releases, calendar of upcoming events, and the NTP Update quarterly newsletter.

The public and other interested parties can stay abreast of NTP activities and events by subscribing to the NTP listserv, an email notification system (*http://ntp.niehs.nih.gov/go/getnews*). In addition, requests for information can be made to the Central Data Management office (CDM@niehs.nih.gov or 919-541-3419), or through Freedom of Information Act requests (*http://www.niehs.nih.gov/about/od/ocpl/foia/contact/index.cfm*).

As always, NTP welcomes input on its programs and priorities. This input can be through response to formal requests for public comment in Federal Register notices, or informal submissions to the Office of Liaison, Policy, and Review, NIEHS/NTP (919-541-7539 or ntpinfo@niehs.nih.gov).

A. Organizational Structure and Oversight

Three agencies form the core for NTP (Figure 1): the National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention, the U.S. Food and Drug Administration (FDA), primarily through its National Center for Toxicological Research (NCTR), and the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health.

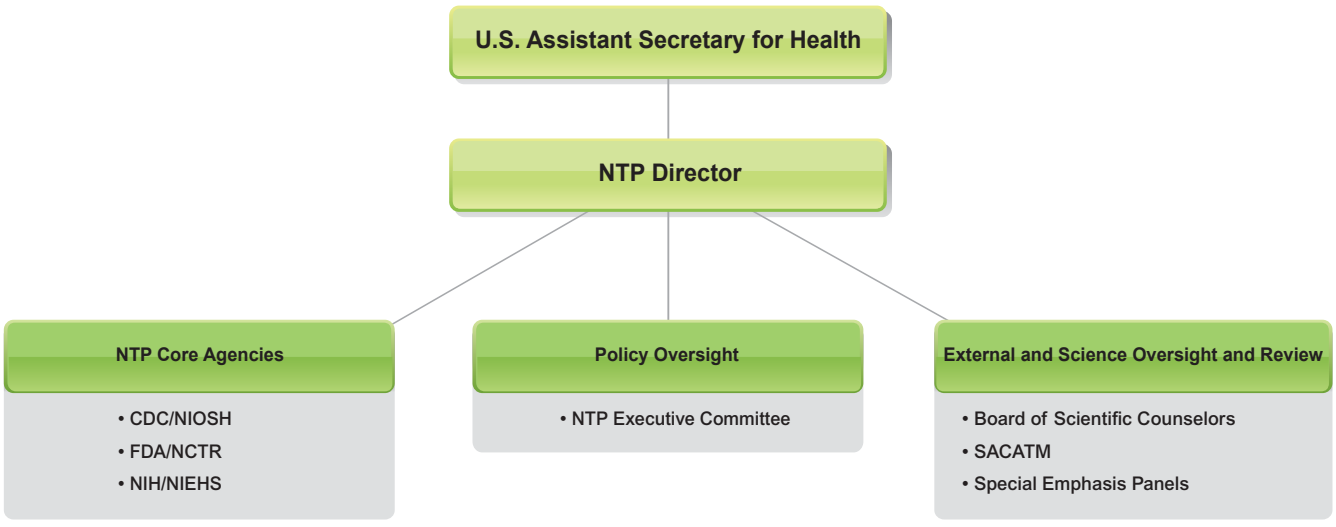
NTP is located administratively at NIEHS, and Linda Birnbaum, Ph.D., serves as director of NIEHS and NTP. John Bucher, Ph.D., is the NTP associate director, and director of the NTP Division at NIEHS, herein referred to as NIEHS/NTP, which is the focal point for NTP activities. NIEHS and NTP utilize best research practices and embrace developments in technology to discover how the environment affects people, and seek to lead the field of environmental health sciences in innovation and the application of research to solve health problems.

John Howard, M.D., is the director of NIOSH, and Gayle DeBord, Ph.D., associate director for science in the Division of Applied Research and Technology, manages the NTP program within NIOSH, herein referred to as NIOSH/NTP. Staff from the following NIOSH divisions participate in NTP activities: Division of Surveillance, Hazard Evaluations, and Field Studies; Division of Applied Research and Technology; Education and Information Division; and Health Effects Laboratory Division.

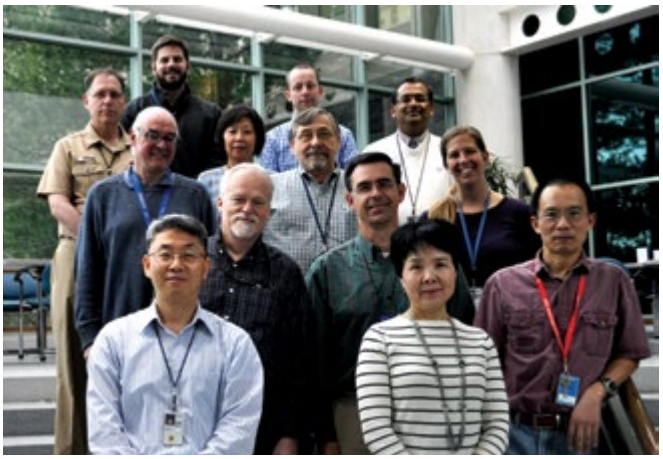
The mission of NIOSH is to generate new knowledge in the field of occupational safety and health, and to transfer that knowledge into practice for the betterment of workers. NIOSH participation in NTP is consistent with its mandate to protect workers' health and safety, under the Occupational Safety and Health Act and the Federal Mine Safety and Health Act.

William Slikker Jr., Ph.D., is the director of NCTR, and Paul Howard, Ph.D., associate director of the Office of Scientific Coordination, manages the NTP program within NCTR, herein referred to as NCTR/NTP. NCTR staff scientists, in partnership with researchers from elsewhere in FDA, other government agencies, academia, and industry, provide innovative technology, methods development, vital scientific training, and technical expertise. NCTR conducts an array of studies that reflect the NTP mission, and is critical in supporting FDA product centers and their regulatory roles.

Figure 1. Organizational Structure of NTP



NIEHS/NTP Staff



NIOSH Staff: Health Effects Laboratory Division

NIOSH Staff: Division of Applied Research and Technology and the Division of Surveillance, Hazard Evaluations, and Field Studies

NIOSH Staff: Education and Information Division

NCTR/NTP Staff

NCTR/NTP Staff

B. Training Programs

NTP offers a limited number of postdoctoral training fellowships that prepare scientists for careers in pharmaceutical and chemical industries, regulatory agencies, and academia. Full details on opportunities, benefits, and applications can be found at *http://www.niehs.nih.gov/careers/research/postdoc-training/index.cfm*. The training program falls into the following six areas: applied toxicology and carcinogenesis, biomolecular screening and computational toxicology, health assessment and translation, laboratory animal medicine, systems and mechanistic toxicology, and toxicological pathology. In FY 2013, NTP staff mentored 20 postdoctoral fellows at NIEHS.

Table 1. NTP Training Program Postdoctoral Fellows in FY 2013

Training Program	Fellow
Applied toxicology and carcinogenesis	Kristen Ryan
	Brian Sayers
	In Ok Surh
	Sheetal Thakur
Biomolecular screening and computational toxicology	Rachel Goldsmith
	Julie Hall
	Jui-Hua Hsieh
	Yang Sun
Health assessment and translation	Katie Pelch
Laboratory animal medicine	Sheba Churchill
Systems and mechanistic toxicology	Xiaohua Gao
	Ntube Ngalame
	Ruben Orihuela-Garcia
	Rachel Person
	Yuanyuan Xu
Toxicological pathology	Sachin Bhusari
	Michael Boyle
	Michelle Cora
	Tanasa Osborne
	Erin Quist

C. Advisory Boards and Committees

NTP receives policy guidance, science oversight, and peer review from formal external groups, including the NTP Executive Committee, NTP Board of Scientific Counselors, and Scientific Advisory Committee on Alternative Toxicological Methods. Ad hoc special emphasis panels also help guide NTP activities.

i. NTP Executive Committee

The NTP Executive Committee provides programmatic and policy oversight to the NTP director. The Executive Committee meets once or twice a year in closed forum. Members of this committee include the heads, or their designees, from the following federal agencies:

- U.S. Consumer Product Safety Commission (CPSC)
- U.S. Department of Defense (DOD)
- U.S. Environmental Protection Agency (EPA)
- U.S. Food and Drug Administration (FDA)
- National Cancer Institute (NCI)
- National Center for Environmental Health/Agency for Toxic Substances and Disease Registry (NCEH/ATSDR)
- National Institute of Environmental Health Sciences (NIEHS)
- National Institute for Occupational Safety and Health (NIOSH)
- Occupational Safety and Health Administration (OSHA)

To enhance agency interactions, NTP uses agency points of contact, in lieu of formal committees, to streamline communication. Agency points of contact have a dedicated responsibility and time commitment; are knowledgeable about the NTP mission, programs, and their agency's resources; and allow the most relevant agency expertise to be brought to bear on NTP issues.

ii. NTP Board of Scientific Counselors

The NTP Board of Scientific Counselors (BSC), a federally chartered advisory group, provides scientific oversight to NTP on the scientific merit of its programs and activities. The HHS Secretary appoints members to the BSC. The BSC can consist of up to 35 scientists, primarily from the public and private sectors, with scientific expertise relevant to NTP activities. The BSC charter and current roster are available at *http://ntp.niehs.nih.gov/go/164*. Lori White, Ph.D., designated federal officer, manages the BSC. **Table 2** provides the roster for FY 2013.

BSC members and NTP staff at the June 2013 BSC meeting

The BSC met twice in FY 2013 (*http://ntp.niehs.nih.gov/go/9741*). At the meeting on Dec. 11, 2012, the BSC reviewed a draft testing concept for polycyclic aromatic hydrocarbons. The BSC was updated on the "NTP Approach for Systematic Review and Evidence Integration for Literature-based Health Assessments," and heard a report from the chair of the BSC working group that evaluated the draft approach. NTP provided updates on studies on bisphenol A (BPA) and on NTP progress since the June 2012 meeting, from the NIEHS and NTP director and NTP associate director.

The second BSC meeting was held June 25, 2013. The BSC voted unanimously to approve concepts for contracts regarding quality assessment support and global pathology support. NTP staff presented a report on the Report on Carcinogens (RoC) peer-review meeting on 1-bromopropane and cumene, held March 2013. Office of Health Assessment and Translation (OHAT) staff briefed the BSC on the "NTP Monograph on Developmental Effects and Pregnancy Outcomes Associated With Cancer Chemotherapy Use During Pregnancy," and on the revised approach on systematic review published for public comment in February 2013. The BSC reviewed a draft RoC concept on "Shift Work at Night, Light at Night, and Circadian Disruption," and heard about planned OHAT activities. The NIEHS and NTP director and NTP associate director provided reports updating the BSC on NTP progress since the December 2012 meeting.

Table 2. NTP Board of Scientific Counselors Membership Roster FY 2013

Name and Title	Affiliation	Term Ends
Robert E. Chapin, Ph.D. Laboratory Director	Pfizer Groton, Connecticut	06/30/15
George B. Corcoran, Ph.D., A.T.S. Chair and Professor Department of Pharmaceutical Sciences Eugene Applebaum College of Pharmacy and Health Sciences	Wayne State University Detroit, Michigan	06/30/16
David C. Dorman, D.V.M., Ph.D. Professor College of Veterinary Medicine	North Carolina State University Raleigh, North Carolina	06/30/15
David A. Eastmond, Ph.D. (chair, 2012) Professor and Chair Department of Cell Biology and Neuroscience	University of California Riverside, California	12/27/12
Elaine M. Faustman, Ph.D. Professor and Director Institute for Risk Analysis and Risk Communication Department of Environmental and Occupational Health Sciences	University of Washington Seattle, Washington	12/27/12
Miguel C. Fernandez, M.D., F.A.C.E.P., F.A.A.E.M., F.A.C.M.T., F.A.A.C.T. Professor of Surgery Division of Emergency Medicine Director, South Texas Poison Center	University of Texas Health Science Center San Antonio, Texas	12/27/13
Jack R. Harkema, D.V.M., Ph.D., D.A.C.V.P. Distinguished Professor Department of Pathobiology and Diagnostic Investigation	Michigan State University East Lansing, Michigan	06/30/15
Dale Hattis, Ph.D. Research Professor George Perkins Marsh Institute	Clark University Worcester, Massachusetts	06/30/15
Dana Loomis, Ph.D. Professor and Chair Department of Epidemiology	University of Nebraska Medical Center Omaha, Nebraska	12/27/12
Stephen W. Looney, Ph.D. Professor Department of Biostatistics Department of Oral Health and Diagnostic Science	Georgia Health Sciences University Augusta, Georgia	12/27/12
Melissa A. McDiarmid, M.D., M.P.H. (chair, 2013) Professor of Epidemiology and Preventive Medicine Director, Occupational Health Program	University of Maryland School of Medicine Baltimore, Maryland	12/27/13

Name and Title	Affiliation	Term Ends
Lisa Minor, Ph.D. Consultant	In Vitro Strategies, LLC Flemington, New Jersey	12/27/13
Richard Miller, D.V.M., Ph.D. Vice President Safety Assessment	GlaxoSmithKline Research Triangle Park, North Carolina	12/27/13
Lisa A. Peterson, Ph.D. Professor Division of Environmental Health Sciences and Masonic Center School of Public Health	University of Minnesota Minneapolis, Minnesota	06/30/16
Sonya Sobrian, Ph.D. Associate Professor Department of Pharmacology	Howard University Washington, D.C.	06/30/15
Iris G. Udasin, M.D. Professor Department of Environmental and Occupational Medicine Robert Wood Johnson Medical School	University of Medicine and Dentistry of New Jersey Piscataway, New Jersey	06/30/16
Judith Zelikoff, Ph.D. Professor of Environmental Medicine Director, Community Outreach	New York University School of Medicine Tuxedo, New York	12/27/12
Robert E. Chapin, Ph.D. Laboratory Director	Pfizer Groton, Connecticut	06/30/15

iii. Scientific Advisory Committee on Alternative Toxicological Methods

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) is a federally chartered advisory committee established Jan. 9, 2002, in response to the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Authorization Act of 2000 (42 U.S.C. 285l-3(d)). SACATM advises ICCVAM, the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), and the director of NIEHS and NTP regarding statutorily mandated duties of ICCVAM and activities of NICEATM (see **page 66**). SACATM provides advice on priorities and activities related to the development, validation, scientific review, regulatory acceptance, implementation, and national and international harmonization of new, revised, and alternative toxicological test methods. The SACATM charter and current roster are available at *http://ntp.niehs.nih.gov/go/167*. **Table 3** provides the roster for FY 2013. SACATM typically meets once a year and members serve rotating terms of up to four years. Lori White, Ph.D., designated federal officer, manages SACATM.

SACATM met once during FY 2013 on Sept. 24, 2013, at NIEHS (*http://ntp.niehs.nih.gov/go/8202*). At the meeting, ICCVAM and NICEATM updated SACATM on the new vision, direction, and procedures for ICCVAM and on activities by NICEATM. An overview and strategy were presented for ICCVAM to utilize adverse outcome pathways, followed by current NICEATM projects related to the skin sensitization adverse outcome pathway. NTP staff presented updates on Tox21 activities and on collaborations through the International Cooperation on Alternative Test Methods (ICATM) memorandum. ICCVAM members presented reports on two international workshops: Alternative Methods for Leptospira Vaccine Potency Testing and Alternative to the Murine Histamine Sensitization Test (HIST) for Acellular Pertussis Vaccines.

Members of SACATM and ICCVAM, and NIEHS and NTP staff at the September 2013 SACATM meeting

Table 3. NTP SACATM Membership Roster FY 2013		
Name and Title	**Affiliation**	**Term Ends**
Lauren E. Black, Ph.D. Senior Scientific Advisor Navigators Services	Charles River Laboratories Reno, Nevada	11/30/16
Tracie E. Bunton, D.V.M., Ph.D. Consultant	Eicarte LLC Gettysburg, Pennsylvania	06/30/15
Joy Cavagnaro, Ph.D., D.A.B.T., R.A.C., A.T.S., R.A.P.S. President and Founder	Access BIO, L.C. Boyce, Virginia	11/30/14
Joan M. Chapdelaine, Ph.D. Consultant	Scott Township, Pennsylvania	06/30/15
Mark G. Evans, D.V.M., Ph.D., A.C.V.P. Research Fellow La Jolla Laboratories	Pfizer San Diego, California	06/30/15
Michael D. Kastello, D.V.M., Ph.D. Vice President and Global Head Animal Research and Welfare Disposition, Safety and Animal Research	Sanofi Bridgewater, New Jersey	11/30/16
Safdar A. Khan, D.V.M., M.S., Ph.D., D.A.B.V.T. Senior Toxicologist Senior Director of Toxicology Research	ASPCA Animal Poison Control Center Urbana, Illinois	11/30/16
Steven M. Niemi, D.V.M. (chair) Director Center for Comparative Medicine	Massachusetts General Hospital Charlestown, Massachusetts	06/30/13
Ricardo Ochoa, D.V.M., Ph.D., A.C.V.P. President and Principal	Pre-Clinical Safety, Inc. Niantic, Connecticut	11/30/14

Name and Title	Affiliation	Term Ends
Michael J. Olson, Ph.D., A.T.S. Director Occupational Toxicology Corporate Environment, Health, Safety and Sustainability	GlaxoSmithKline Research Triangle Park, North Carolina	06/30/13
Linda A. Toth, D.V.M., Ph.D. Associate Dean for Research and Faculty Affairs Professor, Department of Pharmacology	Southern Illinois University School of Medicine Springfield, Illinois	06/30/13
Daniel M. Wilson, Ph.D., D.A.B.T. Mammalian Toxicology Consultant Toxicology and Environmental Research and Consulting	The Dow Chemical Company Midland, Michigan	11/30/14
Marilyn Wind, Ph.D. Consultant	Bethesda, Maryland	06/30/15

Interagency Coordinating Committee on the Validation of Alternative Methods

ICCVAM is a permanent interagency committee of NIEHS under NICEATM. The committee was formally established by the ICCVAM Authorization Act of 2000 (42 U.S.C. 285l-3). Its purpose is to establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new or revised scientifically valid toxicological tests that protect human and animal health and the environment, while reducing, refining, or replacing animal tests and ensuring human safety and product effectiveness (see *http://iccvam.niehs.nih.gov/about/about_ICCVAM.htm*). Members of this committee include representatives from the following federal agencies:

- U.S. Consumer Product Safety Commission (CPSC)
- U.S. Department of Agriculture (USDA)
- U.S. Department of Defense (DOD)
- U.S. Department of Energy (DOE)
- U.S. Department of Health and Human Services (HHS)
    - Centers for Disease Control and Prevention (CDC)
        - Agency for Toxic Substances and Disease Registry (ATSDR)
        - National Institute for Occupational Safety and Health (NIOSH)
    - U.S. Food and Drug Administration (FDA)
    - National Institutes of Health (NIH)
        - National Cancer Institute (NCI)
        - National Institute of Environmental Health Sciences (NIEHS)
        - National Library of Medicine (NLM)
        - Office of the Director (OD)
- U.S. Department of the Interior (DOI)
- U.S. Department of Labor (DOL)
    - Occupational Safety and Health Administration (OSHA)
- U.S. Department of Transportation (DOT)
- U.S. Environmental Protection Agency (EPA)

iv. Special Emphasis Panels

NTP uses ad hoc scientific panels, referred to as special emphasis panels, to provide independent scientific peer review and advice on targeted issues, such as agents of public health concern, new and revised toxicological test methods, or other issues. These panels help ensure transparent, unbiased, and scientifically rigorous input to the program for its use in making credible decisions about human health hazards, setting research and testing priorities, and evaluating test methods for toxicity screening.

NTP Technical Reports Peer Review Panels

NTP Technical Reports (TRs) are publications of the results of long-term studies, generally two-year rodent toxicology and carcinogenesis studies. NTP convenes an external, scientific panel to peer review draft NTP TRs at a public meeting, with opportunity for public comment, at NIEHS. The panels are charged to peer review the scientific and technical elements of the study and their presentation; and determine whether the study's experimental design and conduct support the NTP conclusions regarding the carcinogenic activity of the substance tested. There were no TR meetings in FY 2013. Additional information about TR review panel meetings is available at *http://ntp.niehs.nih.gov/go/36051*.

NTP Monographs Peer Review Panels

Monographs are publications on a single, detailed specific topic. On Oct. 1–2, 2012, NTP convened an external, scientific panel at NIEHS to peer review the "Draft NTP Monograph on Developmental Effects and Pregnancy Outcomes Associated With Cancer Chemotherapy Use During Pregnancy." The meeting was open to the public with time scheduled for oral public comment. The panel was charged to determine whether the scientific information cited in the draft monograph is technically correct, clearly stated, and objectively presented; and determine whether the scientific evidence presented in the draft monograph supports the NTP interpretation of the developmental effects and pregnancy outcomes associated with cancer chemotherapy use during pregnancy. The review covered the document's main findings, cancer chemotherapy agents by mechanism of action, long-term evaluations of growth and development, pregnancy outcomes of medical personnel, and background information on cancer diagnosis during pregnancy. The peer-review panel included individuals with expertise in obstetrics and gynecology, developmental biology, gynecological cancers, breast cancer, hematological cancers, epidemiology, and pharmacology. Mary Wolfe, Ph.D., served as the designated federal official for the peer-review meeting. After the meeting, the panel's input was considered in finalizing the monograph. Additional information about this past meeting and other NTP monograph peer-review meetings is available at *http://ntp.niehs.nih.gov/go/36639*.

Report on Carcinogens Peer Review Panels

Report on Carcinogens (RoC) monographs are prepared for each candidate substance selected for review. NTP follows an established, four-part process for preparation of the RoC. More information can be found at *http://ntp.niehs.nih.gov/go/rocprocess* and on **page 23**. On March 21-22, 2013, NTP convened an external, scientific panel at NIEHS to peer review the draft RoC monographs for 1-bromopropane and cumene. The meeting was open to the public with time scheduled for oral public comment. Draft RoC monographs were prepared for each substance, which consisted of a cancer evaluation component and a substance profile. For the draft cancer evaluation component, the panel was charged to comment on whether it is technically correct and clearly stated, whether NTP objectively presented and assessed the scientific evidence, and whether the scientific evidence is adequate for applying the listing criteria. For the draft substance profiles, the panel was charged to comment on whether the scientific justification presented supports the NTP preliminary policy decision on the RoC listing status of the candidate substance.

The panel voted on the NTP draft level of evidence for carcinogenicity determination, based on the available scientific evidence in experimental animals and whether the information cited in the draft substance profile supported the NTP preliminary listing recommendation for the substance in the RoC. The review individually covered the chemical properties and human exposure, disposition and toxicokinetics, studies in experimental animals, mechanistic data and other relevant effects, an overall cancer evaluation, and the draft substance profile, for both 1-bromopropane and cumene. Lori White, Ph.D., served as the designated federal officer for the peer-review meeting. After the meeting, the input from the panel was considered in finalizing the monographs. Additional information about this meeting and other RoC monograph peer-review meetings is available at *http://ntp.niehs.nih.gov/go/38853*.

2. Funding

Current and Projected Research Capacity

NTP relies on voluntary allocations from the program's three core agencies, NIEHS, FDA/NCTR, and NIOSH, to support its activities. These allocations are specified after annual appropriations have been determined. As shown in Figure 2, the total NTP budget for FY 2013 was $121.3 million.

NTP conducts its research studies through contract laboratories, in-house at these three core agencies, or through interagency agreements with other agencies (see **page 15**). In FY 2013, NIEHS funded 32 contracts (see **Table 4**), and held one workshop (see **page 66**), two special emphasis expert panel peer review meetings (see **page 12**), and three scientific advisory meetings (see **pages 7–9**) for NTP.

Figure 2: Past, Current, and Projected Budget

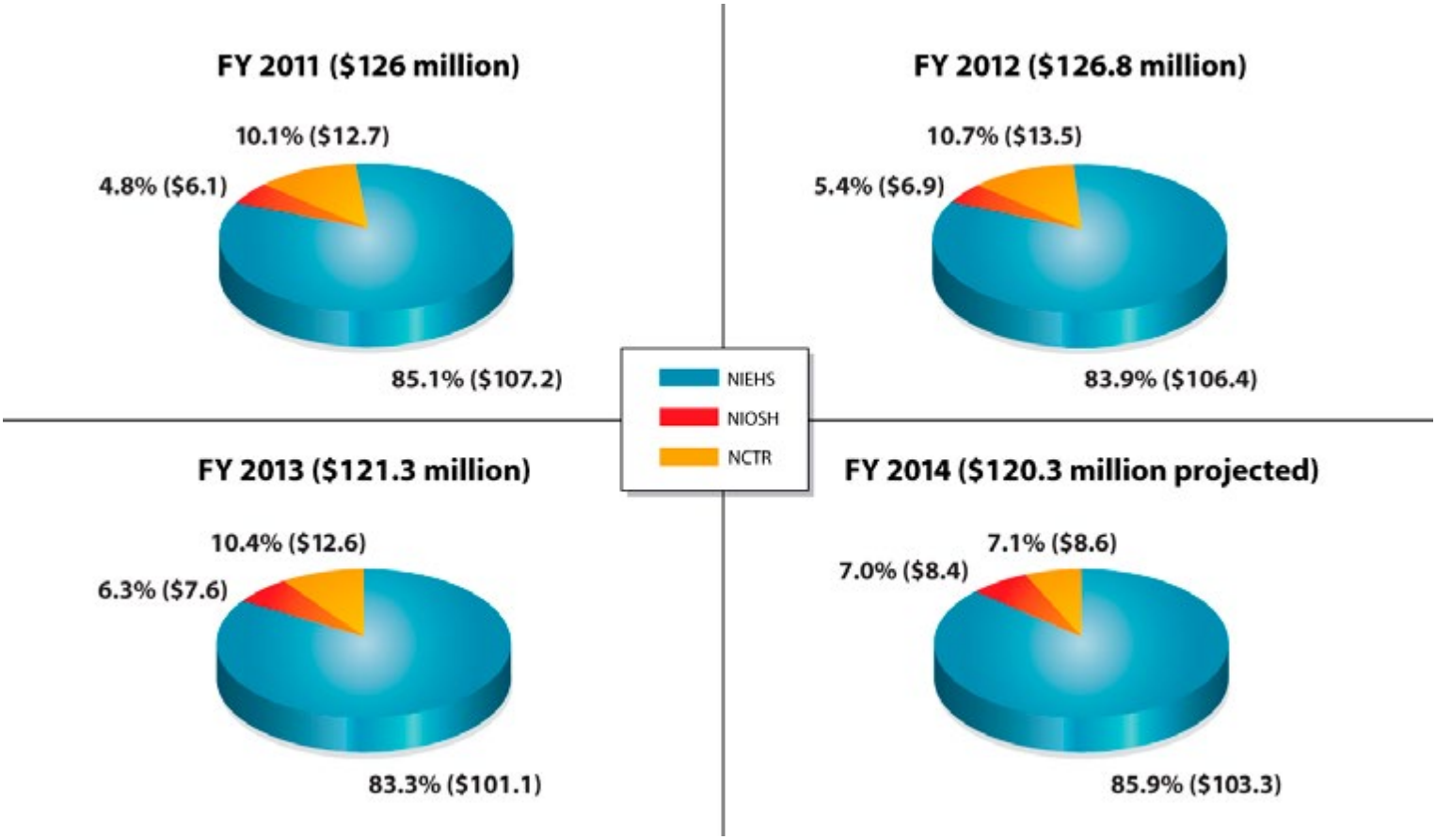


Table 4. NTP Contracts That Supported NTP Testing Activities in FY 2013	
Description	**Contractor**
ADME Chemical Disposition in Mammals	Lovelace Biomedical
	Research Triangle Institute
Analytical Chemistry Support Services	Battelle Memorial
	Midwest Research Institute
	Research Triangle Institute
Archives and Specimen Repository	Experimental Pathology Labs
Bioinformatics Methylation Project	Murdock Research Institute
Chemical Sample Analysis (SEARCH Project)	UNC-Chapel Hill
Evaluate Toxicity Following Early Life Exposure	Southern Research Institute
Evaluation of Alternative Toxicological Methods	Integrated Laboratory Systems
Evaluation of the Toxicity of Selected Chemicals	Battelle Memorial
Genetic Toxicity	Integrated Laboratory Systems
Genetic Toxicity Testing Support Services	Integrated Laboratory Systems
In Life Data Collection and Management System	INSTEM LSS
Investigative Research Support	Integrated Laboratory Systems
NTP Computer and User Support	Vistronix Inc.
NTP Information Systems Support	Scimetrika
NTP Statistical and Computer Support	SRA International
NTP Technical Reports Preparation Support Services	Biotechnical Sciences, Inc.
OHAT Literature-Based Evaluations	ICF Inc.
Pathology Support	Charles River Laboratories
	Integrated Laboratory Systems
Pathology Support and Quality Assessment	Experimental Pathology Labs
Provantis Software	INSTEM
Quality Assurance Oversight of NTP Toxicology Data System Validation	Labscience
Quality Assessment Support/Audits and Inspections	Dynamac
Reproductive Assessments by Continuous Breeding	Research Triangle Institute
Research on Inhalation Toxicology of Environmental Chemicals	Alion Science and Technology
Support for GeneCo Databases	Thomson Reuters
Support for MATLAB	LCS
Support for Preparation of the Report on Carcinogens	Integrated Laboratory Systems
Toxicological and Carcinogenic Potential of Test Agents	Battelle Memorial

Interagency Agreements

In FY 2013, NIEHS provided support for NTP activities through interagency agreements with NCTR and NIOSH. Beginning in 1992, NIEHS established an interagency agreement with FDA, to support collaborative toxicology studies on FDA-regulated agents that were nominated to NTP. This support has been primarily to study chemicals where FDA has no legal authority to require the regulated community to provide toxicological data for a product. This agreement has led to investigations of mechanisms of action, and assessments

of toxicity for many classes of chemicals, including cosmetics, endocrine-disrupting compounds, food contaminants, food cooking byproducts, dietary supplements, drugs, and anesthetics. The studies are conducted at NCTR. In addition, the interagency agreement partially supports the NCTR Office of Regulatory Affairs Phototoxicity Research and Testing Laboratory.

In 1997, NIEHS established an interagency agreement with NIOSH for NTP studies to characterize and evaluate adverse effects of complex occupational exposures. For a comprehensive assessment of occupationally relevant exposures, NTP and NIOSH coordinate efforts to increase knowledge, identification, and education of occupational health research. NIOSH and NTP also work together to support immunotoxicology projects, evaluating adverse health effect to the immune system from environmental exposure to chemical or physical agents.

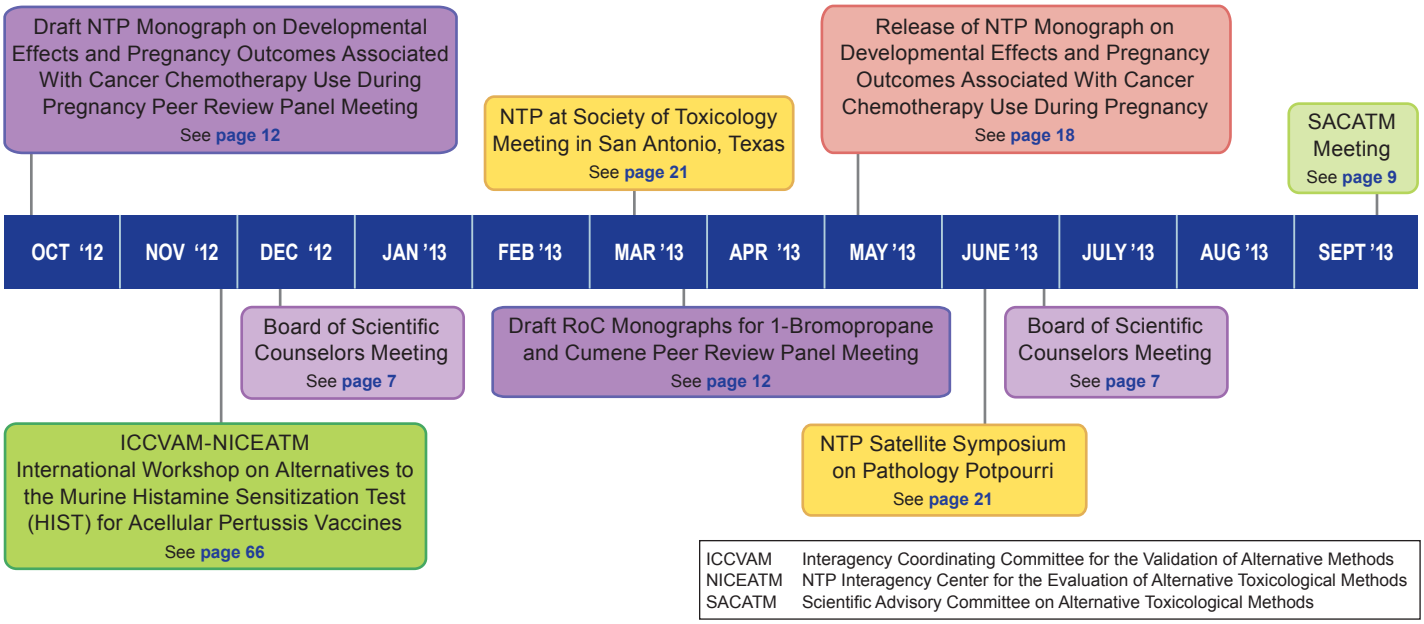
In 2007, NIEHS established an interagency agreement with the National Human Genome Research Institute and its NIH Chemical Genomics Center (NCGC) to support high throughput screening activities for the collaborative Tox21 program. NIH reorganization in 2012 placed the NCGC within the newly created National Center for Advancing Translational Sciences (NCATS), moving the NTP interagency agreement to be with NCATS. Screening efforts are aimed at providing data for use in toxicity profiling, and for prioritization of substances for further in-depth toxicological evaluation, identification of mechanisms of action requiring further investigation, and development of predictive models for in vivo biological response. The use of high throughput and high content screening assays will increase testing throughput, provide greater coverage of chemical and biological space, and decrease the cost of testing potentially toxic compounds. To accomplish these goals, NTP provided sets of compounds, to be incorporated into the comprehensive Tox21 10,000-compound library, for testing in a battery of high throughput and high content screens that were selected by the NCATS laboratory in consultation with NTP. All test data generated from this effort will be deposited into one or more public databases, such as PubChem.

Also in 2008, NIEHS and EPA signed the Phthalate Initiative interagency agreement, to address nominations of bis(2-ethylhexyl) phthalate and other phthalates to NTP for testing. Some of the study findings from this interagency agreement, which came to an end in FY 2011, were published in FY 2013.

3. NTP Highlighted Activities

Figure 3 displays the major events for NTP from FY 2013. Below are additional activities of importance from FY 2013.

Figure 3: FY 2013 Highlights



A. Nonneoplastic Lesion Atlas

In FY 2013, NTP prepared for the launch of the NTP Nonneoplastic Lesion Atlas, a Web-based resource that contains hundreds, and eventually thousands, of high-quality images and guidelines for nonneoplastic lesions in experimental rodent models. While nonneoplastic lesions are not cancerous, nonneoplastic diseases, such as cardiovascular and pulmonary diseases, are a major cause of illness and death, and many are thought to have environmental causes. For example, forms of pulmonary fibrosis, a disease that causes lung scarring, have been linked to exposures to inorganic materials, such as asbestos, vanadium, cobalt, nickel, beryllium, and sulfur dioxide, or organic materials, such as dust from cotton, grain, and wood.

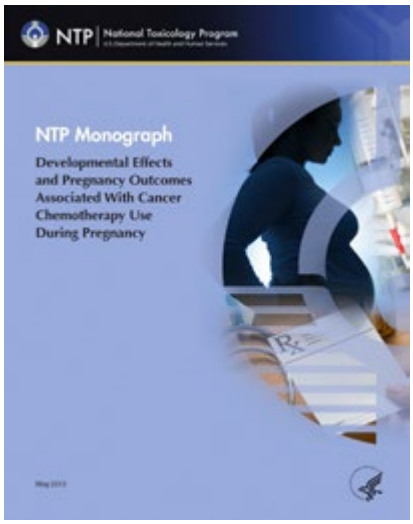
Diagnosing and recording nonneoplastic lesions can be challenging, because terminology and diagnostic strategies can vary among pathologists. The purpose of the Nonneoplastic Lesion Atlas is to standardize the terminology, diagnostic strategy, and recording of nonneoplastic rodent lesions, to improve the consistency, and facilitate database searches, comparisons between studies, and generation of historical control data for nonneoplastic lesions. The NTP Nonneoplastic Lesion Atlas is planned for launch in FY 2014. For more information, see *http://ntp.niehs.nih.gov/nnl*.

B. Realignment of NICEATM and ICCVAM

During its first 15 years, ICCVAM evaluated many alternative methods, and made formal recommendations about their potential regulatory use to federal agencies. However, ICCVAM stakeholders raised concerns that the methods recommended by ICCVAM were not being used for regulatory decision-making. In February 2013, the NIEHS and NTP director announced that NIEHS would move forward with a different philosophy toward ICCVAM, whereby the partner regulatory agencies would drive ICCVAM activities. At the same time, NICEATM would expand its scope to provide bioinformatic and computational toxicology support to NIEHS/NTP.

In response to this new philosophy, ICCVAM developed a draft document entitled "A New Vision and Direction for ICCVAM," which was made available for public comment in August 2013. The document presents the ICCVAM areas of priority and scientific focus for immediate resource investment; plans to improve communications with stakeholders and the public; and interest in exploring new paradigms for the validation and utilization of alternative toxicological methods. ICCVAM is carefully considering public and SACATM comments on the draft document, as it develops new operating procedures and plans activities for the future.

C. Chemotherapy Use During Pregnancy



In May 2013, NTP published the "NTP Monograph on Developmental Effects and Pregnancy Outcomes Associated With Cancer Chemotherapy Use During Pregnancy." Many chemotherapy agents for the treatment of cancer are known mutagens or carcinogens. However, there is a lack of comprehensive reviews on the pregnancy outcomes following cancer chemotherapy use during pregnancy in humans. The monograph provides a comprehensive literature review, including all available human data on follow-up evaluations in offspring who were exposed to chemotherapeutics during gestation. It also includes a review of the developmental toxicity of these agents in laboratory animals, and reports examining their transport via the placenta or breast milk.

Overall, the NTP evaluation found that chemotherapy for treatment of cancer appears to be associated with a higher rate of major malformations following exposure during the first trimester, compared to exposure in the second and/or third trimester only, while the rate of major malformations in the second and/or third trimester was similar to the rate in the general population. There was an increase in the rate of stillbirth following exposure in the second and/or third trimester, and a higher incidence of abnormally low levels of amniotic fluid, which was primarily attributable to one chemotherapy agent (trastuzumab). Chemotherapy for treatment of cancer did not appear to increase spontaneous preterm birth, or impair normal growth and development of offspring during early life. While the monograph does not provide medical advice or guidance, it is intended as a resource for clinicians and their pregnant patients. The "NTP Monograph on Developmental Effects and Pregnancy Outcomes Associated With Cancer Chemotherapy Use During Pregnancy" is available at *http://ntp.niehs.nih.gov/go/36495*.

D. CLARITY-BPA Research Program: Synergizing Academic and Guideline-Compliant Research

NIEHS and FDA have developed a consortium-based research program to improve the link between academic research and guideline-compliant research, to evaluate the low-dose hazard of bisphenol A (BPA). Certain

plastics and epoxy resins contain BPA, and are used to make a variety of common consumer goods, such as water bottles, CDs, DVDs, food containers, beverage cans, and lining for pipes. The Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA) utilizes a unique collaborative approach to fill knowledge gaps, and offers a more comprehensive body of scientific information to better inform risk assessments. Building more effective connections between risk assessors and those who conduct basic hazard identification research could enhance the scientific basis of chemical risk assessments.

NCTR/NTP is conducting a chronic perinatal rodent toxicity study on BPA. NIEHS/NTP is managing consortium activities, and facilitating research by twelve grantees using samples gathered from a guideline-compliant toxicity study. CLARITY-BPA will contribute to the understanding of potential effects of BPA. Another outcome is that the consortium may serve as a new model for filling knowledge gaps, and improving the scientific knowledge base on which regulatory hazard assessments are made. The CLARITY-BPA publication in the journal Reproductive Toxicology is available at *http://www.ncbi.nlm.nih.gov/pubmed/23747832*.

E. Crowdsourcing Human Variability Data

NIEHS, NCATS, the University of North Carolina at Chapel Hill, Sage Bionetworks, and DREAM teamed up to launch an innovative crowdsourced challenge, the NIEHS-NCATS-UNC DREAM Toxicogenetics Challenge, that utilized data collected from the 1000 Genomes Toxicity Screening Project. The NIEHS-NCATS-UNC team conducted the largest ever population-based in vitro cytotoxicity study, to understand how genetic variation affects individual response to common environmental and pharmaceutical chemicals. The study evaluated the extent of cytotoxicity induced in 1,086 human lymphoblastoid cell lines by 179 pharmaceutical or environmental chemicals. The 1,086 cell lines represented nine distinct geographical populations with defined genetic heterogeneity.

The crowdsourced challenge asked participants, who could be anyone with an interest, to use data from the toxicogenetics project to meet two subchallenges:

1. Use the biological data to develop a model that accurately predicts individual responses to chemical exposure.
2. Use the data on chemical properties to develop a model that accurately predicts how a particular population will respond to certain types of chemicals.

The challenge launched in June 2013 and closed in September 2013. There were 99 submissions from 34 teams for subchallenge 1, and 85 submissions from 24 teams for subchallenge 2. The top-scoring teams were announced at the November 2013 DREAM Conference in Toronto. The results of the challenge will be published in the journal Nature Biotechnology.

F. Mouse Methylome Project

The methylome, a component of the epigenome, is one of the factors that may affect susceptibility to cancer and other chemical exposure-related diseases. The methylome is an individual's genome-wide pattern of cytosine methylation, which is the addition of a methyl group to cytosine, one of the four major bases of DNA. Presently, there is no consensus mouse reference database for the methylome, which significantly handicaps an understanding of the mouse model in toxicology and environmentally related diseases, and the designing and conducting of research to understand associated mechanisms.

The Mouse Methylome Project is creating a high-resolution map of the mouse liver methylome from three different mouse strains — two parental strains C57BL/6N and C3H/HeN, and their first generation hybrid

offspring B6C3F1/N. These strains show dramatically different incidences of spontaneous liver tumors, which often confound two-year toxicology and carcinogenesis studies. This variable incidence of liver cancer may be due, in part, to differences in the epigenetic machinery, and also in the sites and amounts of cytosine methylation in critical tumor suppressor genes and other regulatory regions of the genome that affect liver cancer susceptibility and its heritability across generations.

Scientists collected liver samples, as well as samples of four other tissues, including brain, cardiac and skeletal muscle, brown and white fat, and epididymal sperm, from all mice, at the same age, to minimize age as a confounding factor for gene expression and epigenetics. They prepared sequencing libraries of the liver samples, and banked samples of the other four tissue types for future use. In FY 2013, scientists completed characterization of the liver transcriptome, or the collection of RNA in the liver, genomic sequencing, and bisulfite treatment of DNA, to map all methylated sites in the mouse genome. Ongoing bioinformatics analyses found differentially methylated regions related to gender, strain, and heritability, and relationships with gene expression. Analysis efforts will continue in FY 2014.

G. NTP Impact on Regulatory Agencies

Federal and state regulatory agencies use NTP study data and recommendations in considering the need to regulate and test specific chemicals to protect human health. **Table 5** lists NTP data and recommendations used by other agencies in FY 2013.

Table 5. Use of NTP Study Data or Recommendations by Federal and State Regulatory Agencies in FY 2013

Notice	NTP Information Cited	Summary of Notice
California Office of Environmental Health		
Chemical Delisted Effective April 19, 2013 As Known to the State of California to Cause Reproductive Toxicity: Bisphenol A (BPA)	NTP-CERHR (2008). NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A. Research Triangle Park, NC, National Toxicology Program: NIH Publication No. 08 – 5994. NTP (1985) Bisphenol A: reproduction and fertility assessment in CD-1 mice when administered in the feed. NTP-85-192. Research Triangle Park, NC.	Effective April 19, 2013, the Office of Environmental Health Hazard Assessment (OEHHA) is removing BPA (CAS No. 80-05-7) from the list of chemicals known to the State to cause cancer or reproductive toxicity for purposes of Proposition 65. The chemical was added to the list on April 11, 2013, based on reproductive endpoints (developmental toxicity). April 19, 2013 — Proposition 65 *http://oehha.ca.gov/prop65/law/041913BPAdelist.html*
Centers for Disease Control and Prevention		
Final Rule: World Trade Center Health Program; Certification of Breast Cancer in World Trade Center Responders and Survivors Exposed to PCBs	12th edition of the Report on Carcinogens: polychlorinated biphenyls are reasonably anticipated to be a human carcinogen.	On Sept. 12, 2012, HHS published a final rule in the Federal Register adding certain types of cancer to the list of World Trade Center-related health conditions established in the World Trade Center Health Program regulation. April 17, 2013 — 78 FR 22794 *http://www.gpo.gov/fdsys/pkg/FR-2013-04-17/html/2013-09003.htm*

Notice	NTP Information Cited	Summary of Notice
Final Rule: World Trade Center Health Program; Addition of Prostate Cancer to the List of World Trade Center-Related Health Conditions	Report on Carcinogens is a source used in one part of a four-part hierarchical methodology to apply in evaluating whether to propose adding certain types of cancer to the List of World Trade Center-Related Health Conditions included in 42 CFR 88.1 (77 FR 56138, 56142).	On May 2, 2013, the Administrator of the World Trade Center Health Program received a petition (Petition 002) requesting the addition of prostate cancer to the List of World Trade Center-Related Health Conditions (List) covered in the World Trade Center Health Program. In this final rule, the Administrator adds malignant neoplasm of the prostate (prostate cancer) to the List in the World Trade Center Health Program regulations. Sept. 19, 2013 — 78 FR 57505 *http://www.gpo.gov/fdsys/pkg/FR-2013-09-19/pdf/2013-22800.pdf*
Environmental Protection Agency		
Final Rule: 2017 and Later Model Year Light-Duty Vehicle Greenhouse Gas Emissions and Corporate Average Fuel Economy Standards	NTP 11th and 12th editions of the Report on Carcinogens: acetaldehyde and naphthalene are reasonably anticipated to be human carcinogens; benzene, 1,3-butadiene and formaldehyde are known human carcinogens.	EPA and the National Highway Traffic Safety Administration, on behalf of the Department of Transportation, are issuing final rules to further reduce greenhouse gas emissions and improve fuel economy for light-duty vehicles for model years 2017 and beyond. Oct. 15, 2012 — 77 FR 62624 *http://www.gpo.gov/fdsys/pkg/FR-2012-10-15/html/2012-21972.htm*

A complete listing of NTP studies used by federal and state regulatory agencies can be found at *http://ntp.niehs.nih.gov/go/regact*.

H. Additional Activities

NTP participates in a number of meetings with stakeholders and the scientific community. At the 2013 annual meeting of the Society of Toxicology (SOT) in San Antonio, Texas, staff from NIEHS/NTP and other NIEHS staff participated in more than 80 workshops, symposia, and platform sessions; education and information sessions; and poster sessions. Two NTP scientists won prestigious SOT awards: Yuanyuan (Laura) Xu, Ph.D., of the NTP Laboratory received the Best Postdoctoral Publication Award; and Olive Ngalame, Ph.D., also of the NTP Laboratory, won the First Place Stem Cells Specialty Section Postdoctoral Excellence in Research Award. A full listing of the NTP and NIEHS activities at SOT can be found at *http://ntp.niehs.nih.gov/go/35370*.

NTP also hosts symposiums and workshops, to discuss the state of the science and advance the field. For example, the 2013 annual NTP Satellite Symposium, Pathology Potpourri, was held in Portland, Oregon, June 15, in advance of the 32nd annual meeting of the Society of Toxicologic Pathology. The goal of the annual NTP symposium is to present current diagnostic pathology or nomenclature issues to the toxicologic pathology community. “Proceedings of the 2013 Joint JSTP/NTP Satellite Symposium” was published in Toxicologic Pathology, along with summaries of presentations, including diagnostic or nomenclature issues that were presented, along with select images that were used for audience voting and discussion.

NTP also hosted a workshop in FY 2013 related to alternative methods development (see **page 66**).

4. Literature Analysis Activities

NTP conducts literature analysis and review to examine the state of the science and assess if a substance has adverse health effects.

A. Noncancer Health Effects

NTP has made a commitment to studying noncancer health effects. The Office of Health Assessment and Translation (OHAT) within NIEHS/NTP conducts evaluations to assess the evidence that environmental chemicals, physical substances, or mixtures, collectively referred to as substances, cause adverse health effects, and also provides opinions on whether these substances may be of concern, given what is known about current human exposure levels. Assessments of potential adverse effects of environmental substances on reproduction or development, carried out by the Center for the Evaluation of Risks to Human Reproduction from 1998 to 2010, are now undertaken by OHAT, as are workshops and state-of-the-science evaluations to address issues of importance in environmental health sciences. Assessments are published as NTP monographs. The OHAT evaluation process can be found at *http://ntp.niehs.nih.gov/go/38138*. Kristina Thayer, Ph.D., is the director of OHAT.

As highlighted on **page 18**, in FY 2013, OHAT published the "NTP Monograph on Developmental Effects and Pregnancy Outcomes Associated With Cancer Chemotherapy Use During Pregnancy (May 2013)," and continued efforts to incorporate systematic review methodologies into its evaluations (*http://ntp.niehs.nih.gov/go/38673*). **Table 6** lists literature analysis projects that were initiated, ongoing, or completed in FY 2013.

Table 6. NTP Noncancer Health Effects Projects in FY 2013

NTP Project [Study Scientist]	Objective and/or Summary
Completed Project	
Evaluation of Developmental Effects and Pregnancy Outcomes Associated With Cancer Chemotherapy Use During Pregnancy (*http://ntp.niehs.nih.gov/go/36495*) [Howdeshell]	Many chemotherapy agents used to treat cancer are known mutagens or carcinogens. However, there is a lack of comprehensive reviews on the pregnancy outcomes following cancer chemotherapy use during pregnancy in humans. This evaluation published as an NTP monograph provides a comprehensive literature review of the human data, including all available data on follow-up evaluations in offspring who were exposed to chemotherapeutics during gestation. It also included a review of the developmental toxicity of these agents in laboratory animals and any reports examining their transport via the placenta or breast milk.
Ongoing Projects	
Identifying Research Needs for Assessing Safe Use of High Intakes of Folic Acid – State-of-the-Science Evaluation (*http://ntp.niehs.nih.gov/go/38144*) [Boyles]	NTP in conjunction with the NIH Office of Dietary Supplements, is planning a workshop to identify research needs, based on consideration of the state of the science related to the safe use of high intakes of folic acid. The benefit of supplemental folic acid for pregnant women to prevent neural tube defects in their children is well established. At the same time, there is interest in understanding potential adverse health impacts from high intakes of folic acid. This project aims to identify research needs and inform the development of a research agenda for evaluating the safe use of high intakes of folic acid.
Draft case-study protocols to assess the systematic review and evidence integration framework [Rooney]	Case studies are being undertaken to determine if additional refinement or revision to the Draft OHAT Approach (February 2013) might be needed. The two case studies are underway to evaluate the evidence regarding the association of (1) bisphenol A (BPA) exposure with obesity; and (2) perfluorooctanoic acid or perfluorooctane sulfonate exposure with immunotoxicity.

B. Report on Carcinogens

The Report on Carcinogens (RoC) is a congressionally mandated listing of substances that either are known to be human carcinogens or may reasonably be anticipated to be human carcinogens; and to which a significant number of persons residing in the United States are exposed [Section 301(b)(4) of the Public Health Services Act, 42 U.S.C. 241(b)(4)].

Each substance listed in the RoC has a profile, which contains the listing status, a summary of the cancer studies supporting the listing status, information on human exposure, and federal regulations to reduce exposure. The RoC is a cumulative report and consists of substances newly reviewed, in addition to those listed in previous editions. The 12th RoC, the latest edition, was published on June 10, 2011. NTP, with assistance from other federal health and regulatory agencies, prepares the RoC for the HHS Secretary. Preparation of the RoC is managed by the Office of the RoC, under the direction of Ruth Lunn, Dr.P.H. Contract support for preparation of the RoC in FY 2013 was provided by Integrated Laboratory Systems Inc.

NTP follows a four-part process for preparing the RoC (*http://ntp.niehs.nih.gov/go/rocprocess*), using established listing criteria (*http://ntp.niehs.nih.gov/go/15209*). The cancer evaluation for each substance is captured in the draft RoC monographs, and summarizes and assesses the information evaluated by NTP in making its preliminary listing decision. On an ongoing basis, NTP solicits comments on nominations and selects nominations for RoC evaluation, referred to as candidate substances.

In FY 2013, the Office of the RoC invited public input on 20 substances nominated for future editions of the RoC (*http://ntp.niehs.nih.gov/go/rocnom*); selected a new candidate topic, shift work at night, light at night, and circadian disruption, for review (see **Table 7**); and prepared and released for public comment draft RoC monographs for four candidate substances: 1-bromopropane, cumene, ortho-toluidine, and pentachlorophenol and byproducts of its synthesis, hereinafter referred to as pentachlorophenol (see **Table 7**). The scientific reviews for the substances 1-bromopropane and cumene have been completed. The draft monographs were peer reviewed by a panel of experts at a public meeting (*http://ntp.niehs.nih.gov/go/38854*), and the final RoC monographs are available on the RoC website (1-bromopropane, *http://ntp.niehs.nih.gov/go/37896*; cumene, *http://ntp.niehs.nih.gov/go/37895*).

The Office of the RoC convened a public webinar in April 2013, to obtain public and scientific input on issues related to human exposure to pentachlorophenol, in particular, exposure to byproducts of its synthesis and the human cancer studies of exposure to pentachlorophenol (*http://ntp.niehs.nih.gov/go/pcpwebinar*). The webinar presentations and discussions help to inform the cancer evaluation of pentachlorophenol. The draft RoC monographs for ortho-toluidine (*http://ntp.niehs.nih.gov/go/37893*) and pentachlorophenol (*http://ntp.niehs.nih.gov/go/37897*) were released for public comment in August 2013, and the peer review of the draft RoC monographs is scheduled for FY 2014. Following completion of the peer review of the monographs, and sharing information on the reviews with NTP advisory committees, the NTP director will submit the substance profiles for the four candidate substances to the HHS Secretary for review and approval. Preparation of the draft monograph on trichloroethylene is ongoing.

Table 7. Candidate Substances for the RoC		
Candidate Substance *CASRN* [Study Scientist]	**Primary Uses/Exposures**	**RoC Review Status**
1-Bromopropane *106-94-5* [Spencer]	A brominated hydrocarbon used as a solvent for cleaning or as adhesives in a variety of industries including spray adhesives (used in foam cushion manufacturing), vapor degreaser (to clean optics, electronics, and metals), aerosol solvents (for aircraft maintenance), and dry cleaning.	Final monograph published Peer-review meeting, March 2013 NTP BSC meeting, June 2013
Cumene *98-82-8* [Jahnke]	An alkylated benzene found in fossil fuels and used primarily to produce phenol and acetone.	Final monograph published Peer-review meeting, March 2013 NTP BSC meeting, June 2013
Pentachlorophenol and Byproducts of Its Synthesis *87-86-5* [Jahnke]	A chlorinated aromatic compound that is primarily used as wood preservatives in the United States. Its use as a wood preservative has been limited to non-residential and non-agricultural applications (such as the treatment of utility poles and cross arms) since 1984.	Draft RoC monograph released for public comment, August 2013
ortho-Toluidine* *95-53-4* [Lunn]	An arylamine used as an intermediate to manufacture herbicides, dyes, pigments and rubber chemicals.	Draft RoC monograph released for public comment, August 2013
Trichloroethylene* *79-01-6* [Lunn]	Halogenated alkene used primarily for degreasing metals.	Draft monograph in preparation
Shift Work at Night, Light at Night, and Circadian Disruption [Lunn]	Circadian disruption occurs when endogenous circadian rhythms, daily and predictable variations in biological, physiological, and behavioral processes, are out of phase with the external environment or with each other. People, by virtue of the nature of their work, lifestyle choices, or residence, are subjected to interruptions in the natural light-dark cycles, leading to the potential for circadian disruption.	Candidate topic selected NTP BSC review of draft concept, June 2013

* Currently listed as *reasonably anticipated to be a human carcinogen* in the RoC.

5. Testing and Research

NTP maintains a balanced research and testing program that provides data addressing a wide variety of issues important to public health. NTP actively seeks to identify and select study chemicals and other substances for which there is insufficient information to adequately evaluate potential human health hazards. The NTP nomination process is open to the public (*http://ntp.niehs.nih.gov/go/nom*), and nominations can be submitted via the NTP website (*http://ntp.niehs.nih.gov/go/27911*). The agencies represented on the NTP Executive Committee also identify and forward nominations to NTP. The review and selection of nominations for study is a multistep process with input from NTP participating federal agencies, the BSC (see **page 7**), and the public (see *http://ntp.niehs.nih.gov/go/156* for details). Research concepts are developed to outline the general elements of a program of study that would address the specific issues that prompted the nomination of a chemical or substance for testing.

A concept for polycyclic aromatic compounds (PACs) was reviewed during the December 2012 BSC meeting (see **page 7**). PACs are ubiquitous environmental contaminants as a result of their natural occurrence in fossil fuel sources, and formation and release during combustion processes. Exposure to PACs is through consumption of PAC-containing foods, such as contaminated seafood and char-grilled meat; non-dietary ingestion, such as house dust; inhalation of polluted air, such as cigarette smoke and diesel exhaust; or dermal contact in an occupational setting, such as road paving and roofing. Some PACs have been associated with various toxicities, such as carcinogenicity, reproductive and developmental toxicity, immunotoxicity, and neurotoxicity. The PAC Mixtures Assessment Program was presented to the BSC to address existing knowledge gaps. Individual PACs, defined mixtures consisting of subsets of individual PACs, and complex PAC-containing mixtures, such as cookstove emissions and coal tar, will be assessed in a battery of in vitro and short-term in vivo assays focused on a broad array of hazard endpoints. Available predictive models of mixture toxicity will be evaluated for utility, by comparing modeled predictions to observed mixture responses. The PAC Mixtures Assessment Program will provide individual chemical hazard characterization data, and inform the refinement and development of cumulative risk assessment methods for PACs.

The full research concepts for substances can be found at *http://ntp.niehs.nih.gov/go/37038*. Questions about the nomination, review, and selection process can be sent to Scott Masten, Ph.D. at masten@niehs.nih.gov.

A. Technical Reports

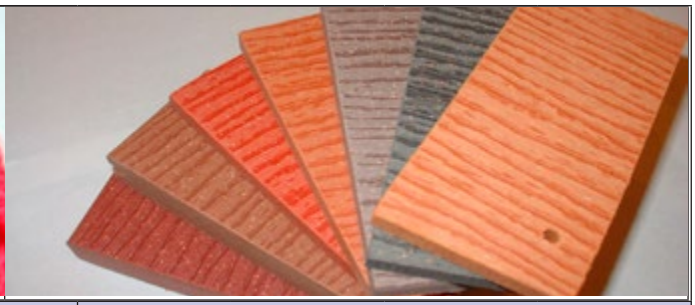
The results of NTP toxicology and carcinogenesis studies undergo rigorous peer review and are published in several NTP report series: Technical Reports (TR), Toxicity Reports (TOX), and Genetically Modified Models Reports (GMM). TRs present the results of NTP long-term, generally two-year, toxicology and carcinogenicity studies. TOX reports are prepared for studies when the substance exposure period is short term, generally up to 13 weeks. GMM reports present the results of substances evaluated by NTP in transgenic mouse strains, such as p53+/- heterozygous and Tg.AC mice. Draft NTP reports undergo peer review by ad hoc scientific panels, or by letter review. All peer reviewers are screened for conflict of interest, prior to confirming their service.

Abstracts and completed TR, TOX, and GMM reports are available on the NTP website (*http://ntp.niehs.nih.gov/go/reports*), and are catalogued in PubMed. Study summaries for other types of studies, such as immunotoxicity, developmental toxicity, and reproductive toxicity, are also available on the NTP study reports page on the website.

Table 8 lists NTP Technical Reports published in FY 2013. NTP used established criteria to evaluate the findings (*http://ntp.niehs.nih.gov/go/baresults*) and determine the strength of the evidence for conclusions regarding the carcinogenic activity of each substance. The conclusions for strength of the evidence for carcinogenic activity are included in the tables. The reports are available at *http://ntp.niehs.nih.gov/*. NTP anticipates eight draft TRs will undergo peer review in FY 2014, as shown in **Table 9**.


Table 8. Technical Reports Published During FY 2013

Chemical/ Exposure – Study Type	Technical Report Number CASRN	Use	Levels of Evidence of Carcinogenic Activity			
			Male Rats	Female Rats	Male Mice	Female Mice
Aloe Vera	TR-577	Recognized as a therapeutic dermatologic agent; extracts incorporated in a variety of topical health care products and cosmetics	Clear Evidence	Clear Evidence	No Evidence	No Evidence
Ginkgo biloba Extract	TR-578 90045-36-6	Herbal supplement	Some Evidence	Some Evidence	Clear Evidence	Clear Evidence
Mixtures of 3′-Azido-3′-Deoxythymidine (AZT), Lamivudine (3TC), Nevirapine (NVP), and Nelfinavir Mesylate (NFV)	TR-569 30516-87-1 134678-17-4 129618-40-2 159989-65-8	Pyrimidine nucleoside analog with antiviral activity used in the treatment of AIDS (Merck 1989)	N/A	N/A	No Evidence (AZT)	Equivocal Evidence (AZT)
					No Evidence (AZT/3TC)	Equivocal Evidence (AZT/3TC)
					Some Evidence (AZT/3TC/ NVP)	Equivocal Evidence (AZT/3TC/ NVP)
					No Evidence (AZT/3TC/ NFV)	No Evidence (AZT/3TC/ NFV)



Chemical/ Exposure – Study Type	Technical Report Number/ CASRN	Use	Levels of Evidence of Carcinogenic Activity			
			Male Rats	Female Rats	Male Mice	Female Mice
Pyrogallol	TR-574 87-66-1	Naturally occurring in food. Used as a modifier in oxidation dyes including hair dyes and colors. Also used as developer in photography; a mordant for dying wool; a reagent for antimony and bismuth; and as a reducer for gold, silver & mercury salts. Used for process engraving and for making colloidal solutions of metals. Used in the manufacture of pharmaceuticals and pesticides. Associated with tobacco: reported either as a natural component of tobacco, pyrolysis product (in tobacco smoke), or additive for one or more types of tobacco products.	No Evidence	No Evidence	Equivocal Evidence	Some Evidence
Trimethylolpropane Triacrylate	TR-576 15625-89-5	Used in the production of ultraviolet-curable inks, electron beam irradiation-curable coatings, and polymers and resins; as a component of photopolymer and flexographic printing plates and photoresists; and as an ingredient in acrylic glues and anaerobic sealants. Also used in paper and wood impregnates, wire and cable extrusion, polymer-impregnated concrete, and polymer concrete structural composites.	Equivocal Evidence	No Evidence	No Evidence	No Evidence

CLEAR Evidence SOME Evidence EQUIVOCAL Evidence NO Evidence

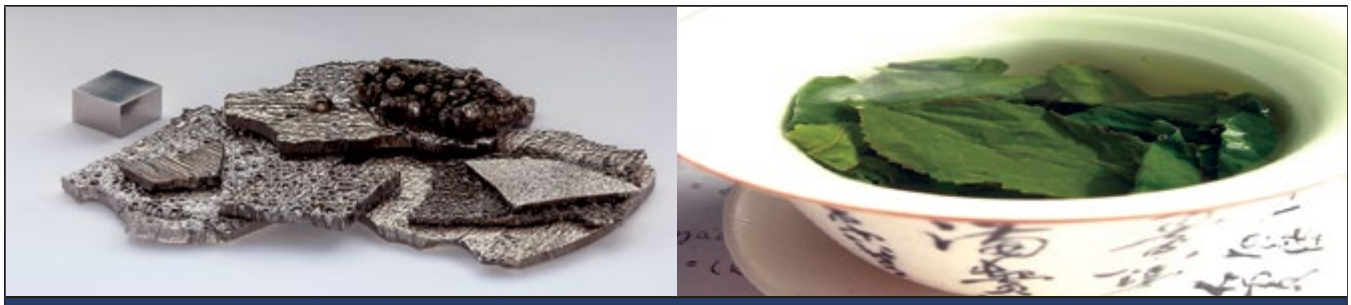


Table 9. Technical Reports Expected to Undergo Peer Review in FY 2014

Chemical	Technical Report Number CASRN	Use
Bromodichloroacetic acid (water disinfection byproduct)	TR-58 71133-14-7	Bromodichloroacetic acid is a water disinfectant byproduct. Naturally occurring bromides in the water participate in the formation of this compound. This chemical is formed after disinfection of water with halogenated oxidants, usually chlorine.
CIMSTAR 3800 (metal working fluid)	TR-586	Semisynthetic; metalworking fluid.
Cobalt	TR-581 7440-48-4	Nuclear medicine and research, industry, paints, water treatment, metallurgy. Associated with tobacco: reported either as a natural component of tobacco, pyrolysis product (in tobacco smoke), or additive for one or more types of tobacco products.
Glycidamide	TR-588 5694-00-8	Metabolite of acrylamide. Associated with tobacco: reported either as a natural component of tobacco, pyrolysis product (in tobacco smoke), or additive for one or more types of tobacco products.
Green tea extract	TR-585	Extract of green tea used as dietary supplement.
Indole-3-carbinol	TR-584 700-06-1	Natural component of Brassica vegetables; marketed as a dietary supplement and cancer preventative agent.
Tetrabromobisphenol A	TR-587 79-94-7	Flame retardant for plastics, paper, and textiles.
Vinylidene chloride	TR-582 75-35-4	Copolymerized with vinyl chloride or acrylonitrile for saran and saran fibers. A widely used chemical intermediate and monomer.

B. NTP Testing

NTP testing program evaluates substances for a variety of health-related effects, generally using rodent models for study. NTP staff develops protocols designed specifically to fully characterize a substance's toxic potential. For each agent studied, a project leader designs a comprehensive testing strategy to address the identified research and testing needs. A project review committee evaluates the testing strategy and proposes an appropriate mechanism for performing the study, such as a grant or contract. The following NTP branches are involved in the testing program: Biomolecular Screening Branch, led by Raymond Tice, Ph.D.; Cellular and Molecular Pathology Branch, led by Robert Sills, D.V.M., Ph.D.; NTP Laboratory, led by Mike Waalkes, Ph.D.; Program Operations Branch, led by Michelle Hooth, Ph.D.; and Toxicology Branch, led by Paul Foster, Ph.D.

i. Disposition, Metabolism, and Toxicokinetic Studies

Complete dosimetry of a chemical or physical agent describes its absorption, distribution, metabolism, and excretion (ADME) in the body, at differing levels of exposure, over all ages, via several routes of exposure, and under varying genetic backgrounds, in humans and test animals. Data from NTP chemical disposition and toxicokinetic studies are used in these studies. Substances evaluated during FY 2013 are listed in **Table 10**. More information can be found at *http://ntp.niehs.nih.gov/go/sp*.

Table 10. Ongoing and Completed Disposition, Metabolism and Toxicokinetic Studies During FY 2013

Chemical	CASRN	Species/Strain	Route	Study Scientist
Bisphenol A	80-05-7	Rats:Sprague Dawley (NCTR)	In-vitro	Delclos
Bisphenol AF	1478-61-1	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Intravenous	Sutherland
2-Butene-1,4-diol	110-64-5	N/A	In-vitro	Doerge
N-Butylbenzenesulfonamide	3622-84-2	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Gavage	Rider
Ephedrine and caffeine combination	N/A	Rats:Wistar Han	Gavage	Dunnick
1,3-Dichloro-2-propanol	96-23-1	Rats:Harlan Sprague Dawley Mice:B6C3F1	Gavage	Waidyanatha
Di(2-ethylhexyl) phthalate	117-81-7	Monkey:Rhesus	Gavage	Delclos
2,2'-Dimorpholinodiethyl ether	6425-39-4	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Dermal	Waidyanatha
2',2'''-Dithiobisbenzanilide	135-57-9	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Gavage	DeVito
2-Ethylhexyl *p*-methoxycinnamate	5466-77-3	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Gavage	McIntyre
Furan	110-00-9	Rats:F344 (NCTR)	Gavage	Walker
Hydroquinone	123-31-9	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Intravenous	DeVito
2-Hydroxy-4-methoxybenzophenone	131-57-7	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Gavage	Auerbach/ McIntyre
Hydroxyurea	127-07-1	Rats:Harlan Sprague Dawley	Gavage	McIntyre
L-beta-Methylaminoalanine	15920-93-1	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Gavage	Ryan
Methylene blue trihydrate	7220-79-3	Rats:F344/N Mice:B6C3F1	Intravenous	Chhabra
Nanoscale silver	7440-22-4	Rats:Harlan Sprague Dawley	Gavage Intravenous	Walker
Octyl salicylate	118-60-5	Rats:Harlan Sprague Dawley	Gavage	Devito

Chemical	CASRN	Species/Strain	Route	Study Scientist
Resveratrol	501-36-0	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Intravenous	Germolec
		Rats:Wistar Han	Gavage	Germolec
Silver acetate	563-63-3	Rats:Harlan Sprague Dawley	Gavage Intravenous	Boudreau
Triclosan	3380-34-5	Mice:B6C3F1/NCTR	Topical application	Fang/ Howard
Tris(2-chloroisopropyl)phosphate	13674-84-5	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Intravenous	Stout
Tris(4-chlorophenyl)methane	27575-78-6	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Intravenous	Surh
Tris(4-chlorophenyl)methanol	3010-80-8	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Gavage	Surh

ii. Genetic Toxicity

Genetic toxicity test results are used to help interpret toxicity, carcinogenicity, or other in vivo test results, and to provide a database for use in structure-activity analyses. Substances tested for genetic toxicity during FY 2013 are listed in **Table 11**. More information can be found at *http://ntp.niehs.nih.gov/go/gt*.

Table 11. Ongoing and Completed Genetic Toxicity Studies During FY 2013

Chemical	CASRN	Testing Battery
3'-Azido-3'-deoxythymidine	30516-87-1	*Salmonella*
Bisphenol AF	1478-61-1	Micronucleus *Salmonella*
Black cohosh	84776-26-1	Micronucleus
Bromodichloroacetic acid	71133-14-7	*Salmonella*
Cell phone radiation (CDMA)	N/A	Micronucleus
Cell phone radiation (GSM)	N/A	Micronucleus
Compound Z	N/A	Micronucleus *Salmonella*
Dimethylamine borane	74-94-2	*Salmonella*
Ethanone, 1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-Tetramethyl-2-Naphthalenyl)- (Iso-E Super [reg]; OTNE)	54464-57-2	*Salmonella*
2-Ethylhexyl p-methoxycinnamate	5466-77-3	Micronucleus
Garcinia cambogia extract	90045-23-1	*Salmonella*
Ionic liquid (1-Butyl-3-methylimidazolium chloride)	79917-90-1	Micronucleus
Ionic liquid (1-Ethyl-3-methylimidazolium chloride)	65039-09-0	Micronucleus
Isopropylated phenol phosphate	68937-41-7	*Salmonella*

Chemical	CASRN	Testing Battery
2-Methyl-6-ethylanline	24549-06-2	*Salmonella*
Nelfinavir	159989-64-7	*Salmonella*
2-Nitro-2-ethyl-1,3-propanediol	597-09-1	*Salmonella*
2-Nitro-1-propanol	2902-96-7	*Salmonella*
Perfluorobutane sulfonate	375-73-5	Micronucleus
Perfluorodecanoic acid	335-76-2	Micronucleus
Perfluorohexane sulfonate potassium salt	3871-99-6	Micronucleus
Perfluorohexanoic acid	307-24-4	Micronucleus
Perfluorononanoic acid	375-95-1	Micronucleus
Perfluorooctane sulfonate	1763-23-1	Micronucleus
Perfluorooctanoic acid	335-67-1	Micronucleus
Potassium hydroxycitrate tribasic monohydrate	232281-44-6	*Salmonella*
Tetrabromobisphenol A	79-94-7	*Salmonella*
Tris(4-chlorophenyl)methane	27575-78-6	*Salmonella*
Tris(4-chlorophenyl)methanol	3010-80-8	*Salmonella*
Wyeth 14,643	50892-23-4	Micronucleus
Zinc carbonate, basic	5263-02-5	Micronucleus

iii. Organ System Toxicity

NTP studies toxicity of environmental substances on organ systems for development, reproduction, and the immune system. **Table 12** lists ongoing and completed organ systems toxicity studies during FY 2013. More information can be found at *http://ntp.niehs.nih.gov/go/type*.

Table 12. Ongoing and Completed Neurotoxicity, Developmental Toxicity and Reproductive Toxicity Studies During FY 2013

Chemical	CASRN	Species/Strain	Route	Study Scientist	Testing Battery
Black cohosh	84776-26-1	Rats:Harlan Sprague Dawley	Gavage	Blystone	Continuous breeding
Butyl paraben (n-Butyl-*p*-hydroxybenzoate)	94-26-8	Rats:Harlan Sprague Dawley	Feed	Blystone	Continuous breeding
Diisobutyl phthalate	84-69-5	Rats:Harlan Sprague Dawley	Feed	Blystone	Continuous breeding
2-Hydroxy-4-methoxybenzophenone	131-57-7	Rats:Harlan Sprague Dawley	Feed	Hansen, Gwinn	Teratology pilot study Developmental toxicity
4-Methylimidazole	822-36-6	Rats:Harlan Sprague Dawley	Feed	Behl	Continuous breeding

Immunotoxicity Testing

NTP immunotoxicity studies address adverse effects on the immune system that may result from exposure to environmental chemicals, biological materials, or therapeutic agents. The identification of substances that have potential to cause injury to the immune system is of considerable public health significance, as alterations in immune function can lead to increased incidence of hypersensitivity disorders, autoimmune or infectious disease, or neoplasia. **Table 13** lists ongoing and completed immunotoxicity studies during FY 2013. More information can be found at *http://ntp.niehs.nih.gov/go/9399*.

Table 13. Ongoing and Completed Immunotoxicity Studies During FY 2013

Chemical	CASRN	Species/ Strain	Route	Study Scientist	Testing Battery
Autumn sunset true color concentrate	N/A	Mice:CBA/ Ca Jackson	Subcutaneous injection	Howard	Hypersensitivity
3'-Azido-3'-deoxythymidine	30516-87-1	Mice:B6C3F1/N	Gavage	Irwin	Immunosuppression–Range finding*, Developmental
Blasting sand (abrasive blasting agents)	N/A	Rats:Harlan Sprague Dawley	Inhalation	Gwinn	Immunosuppression
2,3-Butanedione (Diacetyl)	431-03-8	Mice:BALB/c	Inhalation	Morgan	Immunosuppression–Range finding*
Dermal lotion vehicle development	N/A	Mice:BALB/c	Topical application	Germolec	Hypersensitivity
Dibenz(a,h)anthracene	53-70-3	Mice:B6C3F1/N	Subcutaneous injection	Germolec	Immunosuppression–Range finding*, Immunosuppression–Full protocol**, Developmental
Double dark fudge true color concentrate	N/A	Mice:CBA/ Ca Jackson	Subcutaneous injection	Howard	Hypersensitivity
Double fudge concentrate	N/A	Mice:CBA/ Ca Jackson	Subcutaneous injection	Howard	Hypersensitivity
Echinacea purpurea, extract	90028-20-9	Mice:B6C3F1/N	Gavage	Ryan	Immunosuppression–Full protocol**
Fullerene-C60 (1 micron) (nanoscale material)	99685-96-8	Rats:Wistar Han Mice:B6C3F1	Inhalation	Walker	Immunosuppression–Range finding*
Fullerene-C60 (50 nanometers) (nanoscale material)	99685-96-8	Rats:Wistar Han Mice:B6C3F1	Inhalation	Walker	Immunosuppression–Range finding*
Genistein	446-72-0	Mice:NOD/ MrKTac	Gavage	Germolec	Autoimmunity
Monoclonal antibody protein therapeutics (CD-4)	N/A	Mice:B6C3F1	Intraperitoneal injection	Germolec	Immunosuppression–Full protocol**
Monoclonal antibody protein therapeutics (CD-8)	N/A	Mice:B6C3F1	Intraperitoneal injection	Germolec	Immunosuppression–Full protocol**

Chemical	CASRN	Species/ Strain	Route	Study Scientist	Testing Battery
Nelfinavir mesylate	159989-65-8	Mice:B6C3F1/N	Gavage	Germolec	Immunosuppression – Range finding*; Developmental
Nevirapine	129618-40-2	Mice:B6C3F1	Gavage	Germolec	Developmental
Perfluorodecanoic acid	335-76-2	Rats:Harlan Sprague Dawley	Gavage	Blystone	Immunosuppression
Resveratrol	501-36-0	Mice:NOD/ MrKTac	Gavage	Germolec	Autoimmunity
Rosewood true color concentrate	N/A	Mice:CBA/ Ca Jackson	Subcutaneous injection	Howard	Hypersensitivity
Sodium tungstate, dihydrate	10213-10-2	Mice:B6C3F1/N	Drinking water	Hooth	Immunosuppression– Full protocol**
Specular hematite (abrasive blasting agents)	N/A	Rats:Harlan Sprague Dawley	Inhalation	Gwinn	Immunosuppression
3,3',4,4'-Tetrachloroazobenzene	14047-09-7	Rats:Sprague Dawley	Gavage	Behl	Immunosuppression– Range finding*
		Rats:Crl:CD (Sprague Dawley)	Gavage	Behl	Developmental

* Range finding studies are performed in order to establish the potential effects of a substance on the immune system and to determine doses that could be used in a full immunotoxicology study.

** Full protocols are more comprehensive studies that establish potential adverse effects of a substance on the immune system.

Modified One-generation Reproduction Studies

Classical studies used to evaluate reproductive toxicity are of a multigenerational reproduction experimental design. NTP has modified this classical study design to better utilize the animals produced, and to reduce animal use by improved experimental design and statistical power. **Table 14** lists planned or ongoing modified one-generation studies. More information can be found at *http://ntp.niehs.nih.gov/go/MG*.

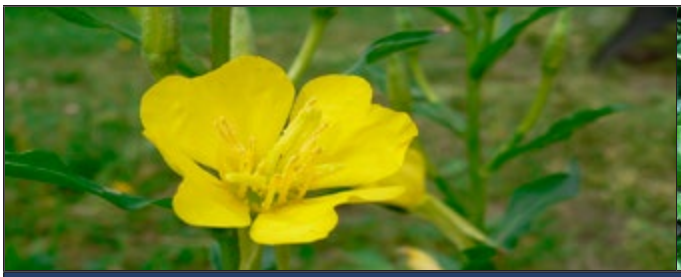



Table 14. Planned or Ongoing Modified One-generation Studies

Chemical	CASRN	Species/ Strain	Study Route	Planned Cohorts	Study Scientist
Bisphenol AF	1478-61-1	Rats:Harlan Sprague Dawley	Feed	Dose range finding[1] Maternal transfer[2] Developmental toxicity[3] Fertility assessment[4] Subchronic toxicity[6]	Sutherland
N-Butylbenzenesulfonamide	3622-84-2	Rats:Harlan Sprague Dawley	Feed	Dose range finding[1] Maternal transfer[2] Developmental toxicity[3] Fertility assessment[4] Neurotoxicity assessment[5] Subchronic toxicity[6]	Rider
Dong quai (*Angelica sinensis*) root extract	299184-76-2	Rats:Harlan Sprague Dawley	Gavage	Dose range finding[1] Developmental toxicity[3] Fertility assessment[4] Neurotoxicity assessment[5] Subchronic toxicity[6]	McIntyre
2-Ethylhexyl *p*-methoxycinnamate	5466-77-3	Rats:Harlan Sprague Dawley	Feed	Dose range finding[1] Maternal transfer[2] Developmental toxicity[3] Fertility assessment[4] Neurotoxicity assessment[5] Subchronic toxicity[6]	McIntyre
Evening primrose oil	90028-66-3	Rats:Harlan Sprague Dawley	Gavage	Dose range finding[1] Developmental toxicity[3] Fertility assessment[4] Subchronic toxicity[6]	Germolec
Garcinia cambogia extract	90045-23-1	Rats:Harlan Sprague Dawley	Feed	Dose range finding[1] Maternal transfer[2] Developmental toxicity[3] Fertility assessment[4] Subchronic toxicity[6]	Rider

Chemical	CASRN	Species/ Strain	Study Route	Planned Cohorts	Study Scientist
Hydroquinone	123-31-9	Rats:Harlan Sprague Dawley	Gavage	Dose range finding[1] Developmental toxicity[3] Fertility assessment[4] Neurotoxicity assessment[5]	DeVito
2-Hydroxy-4-methoxybenzophenone	131-57-7	Rats:Harlan Sprague Dawley	Feed	Dose range finding[1] Developmental toxicity[3] Fertility assessment[4]	McIntyre
Hydroxyurea	127-07-1	Rats:Harlan Sprague Dawley	Gavage	Dose range finding[1] Developmental toxicity[3] Fertility assessment[4] Neurotoxicity assessment[5] Subchronic toxicity[6]	McIntyre
Isopropylphenyl phosphate	68937-41-7	Rats:Harlan Sprague Dawley	Feed	Dose range finding[1] Neurotoxicity assessment[5]	Behl
Perfluorooctane sulfonate	1763-23-1	Rats:Harlan Sprague Dawley	Gavage	Dose range finding[1]	Blystone
Perfluorooctanoic acid	335-67-1	Rats:Harlan Sprague Dawley Mice: CD-1 Reg. [Crl:CD1(ICR)]	Gavage	Dose range finding[1]	Blystone
Sulfolane	126-33-0	Rats: Harlan Sprague Dawley	Drinking water	Dose range finding[1] Developmental toxicity[3] Fertility assessment[4] Neurotoxicity assessment[5] Subchronic toxicity[6]	Blystone
Triphenyl phosphate	115-86-6	Rats:Harlan Sprague Dawley	Feed	Dose range finding[1] Neurotoxicity assessment[5]	Behl
Valerian (*Valeriana oficinalis L.*) root extract (0.8%)	8057-49-6	Rats: Harlan Sprague Dawley	Gavage	Dose range finding[1]	DeVito
Wyeth 14,643	50892-23-4	Rats: Harlan Sprague Dawley Mice: CD-1 Reg. [Crl:CD1(ICR)]	Gavage	Dose range finding[1]	Blystone

[1] Dose range finding: to find the ideal dose for toxicological studies.

[2] Maternal transfer: to study the transfer of chemical from mother to offspring.

[3] Developmental toxicity: to study adverse developmental outcomes such as birth defects.

[4] Fertility assessment: to study adverse effects on fertility in males and females.

[5] Neurotoxicity assessment: to study adverse effects in the structure or function of the central or peripheral nervous system.

[6] Subchronic toxicity: 90-day study of adverse effects in the exposed rodent.

iv. Toxicology/Carcinogenicity Studies

NTP performs appropriate toxicity studies, in part, to provide dose-setting information for chronic studies, and to address specific deficiencies in the toxicology database for the chemical. Toxicology/carcinogenicity studies generally fall into two categories: prechronic toxicity studies, and two-year toxicology and carcinogenicity studies. Studies are generally conducted in rats and mice. Each of these study types is performed according to the "Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological, and Physical Agents in Laboratory Animals for the National Toxicology Program (January 2011)." Additional information can be found at *http://ntp.niehs.nih.gov/go/ba*.

Table 15, **Table 16**, and **Table 17** list the toxicity studies that were ongoing, initiated, and completed during FY 2013. Chronic toxicology/carcinogenicity studies ongoing and initiated in FY 2013 are listed in **Table 18** and **Table 19**.

Table 15. Prechronic Ongoing Toxicology/Carcinogenicity Studies During FY 2013

Study	CASRN	Species/Strain	Study Route	Length	Study Scientist
Bisphenol A	80-05-7	Rats:Harlan Sprague Dawley	Gavage	4 days	DeVito
Cell phone radiation (CDMA)	N/A	Rats:Harlan Sprague Dawley Mice:B6C3F1	Whole body exposure	5 days 49 days 28 days	Wyde
Cell phone radiation (GSM)	N/A	Rats:Harlan Sprague Dawley Mice:B6C3F1	Whole body exposure	5 days 49 days 28 days	Wyde
1-Butyl-3-methylimidazolium chloride (Ionic liquid)	79917-90-1	Rats:Harlan Sprague-Dawley Mice:B6C3F1	Drinking water	90 days	Ryan
1-Butyl-1-methylpyrrolidinium chloride (Ionic liquid)	479500-35-1	Rats:Harlan Sprague-Dawley Mice:B6C3F1	Drinking water	90 days	Ryan
n-Butylpyridinium chloride (Ionic liquid)	1124-64-7	Rats:Harlan Sprague-Dawley Mice:B6C3F1	Drinking water	90 days	Ryan
1-Ethyl-3-methylimidazolium chloride (Ionic liquid)	65039-09-0	Rats:Harlan Sprague-Dawley Mice:B6C3F1	Drinking water	90 days	Ryan
Nanoscale silver	7440-22-4	Rats:Harlan Sprague Dawley (NCTR)	Gavage	13 weeks	Boudreau
Pentabromodiphenyl oxide (technical) (DE 71)	32534-81-9	Rats:Wistar Han	Gavage	GD 6 to PND 21	Dunnick
Tetrabromobisphenol A	79-94-7	Rats:Wistar Han	Gavage	13 weeks	Dunnick

Table 16. Prechronic Toxicology/Carcinogenicity Studies Initiated During FY 2013					
Study	**CASRN**	**Species/Strain**	**Study Route**	**Length**	**Study Scientist**
1-Butyl-3-methylimidazolium chloride (ionic liquid)	79917-90-1	Rats:Harlan Sprague Dawley Mice:B6C3F1	Drinking water	90 days	Ryan
1-Butyl-1-methylpyrrolidinium chloride (ionic liquid)	479500-35-1	Rats:Harlan Sprague Dawley Mice:B6C3F1	Drinking water	90 days	Ryan
n-Butylpyridinium chloride (ionic liquid)	1124-64-7	Rats:Harlan Sprague Dawley Mice:B6C3F1	Drinking water	90 days	Ryan
1-Ethyl-3-methylimidazolium chloride (ionic liquid)	65039-09-0	Rats:Harlan Sprague Dawley Mice:B6C3F1	Drinking water	90 days	Ryan
Pentabromodiphenyl oxide (technical) (DE 71)	32534-81-9	Rats:Wistar Han	Gavage	GD 6 to PND 21	Dunnick
Tetrabromobisphenol A	79-94-7	Rats:Wistar Han	Gavage	13 weeks	Dunnick

Table 17. Completed Prechronic Toxicology/Carcinogenicity Studies During FY 2013					
Study	**CASRN**	**Species/Strain**	**Study Route**	**Length**	**Study Scientist**
Bisphenol A	80-05-7	Rats:Sprague Dawley (NCTR)	Gavage	90 days	Delclos
Black cohosh	84776-26-1	Rats:Harlan Sprague Dawley	Gavage	14 days	Blystone

Table 18. Chronic Toxicity/Carcinogenicity Studies Ongoing During FY 2013					
Study	**CASRN**	**Species/Strain**	**Study Route**	**Length**	**Study Scientist**
Aging cohort study	N/A	Mice:129S1/SvImJ Mice:B6C3F1 (Jackson) Mice:C3H/HeJ Mice:C57BL/6J (Jackson) Mice:CAST/EiJ (*M. m. castaneus*) Mice:NZO/HiLtJ Mice:PWK/PhJ Mice:WSB/EiJ (*M. m. domesticus*) Mice:A/J Mice:NOD. B10Sn-H2(b)/J	N/A	2 years	Wyde
Antimony trioxide	1309-64-4	Rats:Wistar Han Mice:B6C3F1/N	Inhalation	2 years	Stout
Bisphenol A	80-05-7	Rats:Sprague Dawley (NCTR)	Gavage	2 years	Delclos
Black cohosh	84776-26-1	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Gavage	2 years	Blystone
Bromodichloroacetic acid (water disinfection byproduct)	71133-14-7	Rats:F344/NTac Mice:B6C3F1	Drinking water	2 years	DeVito
2,3-Butanedione (Diacetyl)	431-03-8	Rats:Wistar Han Mice:B6C3F1/N	Inhalation	2 years	Morgan
Cell phone radiation (CDMA)	N/A	Rats:Harlan Sprague Dawley Mice:B6C3F1	Whole body exposure	2 years	Wyde
Cell phone radiation (GSM)	N/A	Rats:Harlan Sprague Dawley Mice:B6C3F1	Whole body exposure	2 years	Wyde
p-Chloro-a,a,a-trifluorotoluene	98-56-6	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Inhalation	2 years	Stout
CIMSTAR 3800 (metal working fluid)	N/A	Rats:Wistar Han Mice:B6C3F1/N	Inhalation	2 years	Morgan
Cobalt	7440-48-4	Rats:F344/NTac Mice:B6C3F1	Inhalation	2 years	Behl
Dibutyl phthalate	84-74-2	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Feed	2 years	Blystone
Di(2-ethylhexyl) phthalate	117-81-7	Rats:Harlan Sprague Dawley	Feed	Perinatal and 2 years	Foster
Furan	110-00-9	Rats:F344 (NCTR)	Gavage	2 years	Beland
Glycidamide	5694-00-8	Rats:F344 (NCTR) Mice:B6C3F1/NCTR	Drinking water	2 years	Beland
Green tea extract	N/A	Rats:Wistar Han Mice:B6C3F1	Gavage	2 years	Thakur
2-Hydroxy-4-methoxybenzophenone	131-57-7	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Feed	2 years	McIntyre

Study	CASRN	Species/Strain	Study Route	Length	Study Scientist
Indole-3-carbinol	700-06-1	Rats:Harlan Sprague Dawley Mice:B6C3F1	Gavage	2 years	Wyde
Insertional mutagenesis - definitive vector study	N/A	Mice:C57BL/6	Intravenous	14 months	Germolec
Pentabromodiphenyl oxide (technical) (DE 71)	32534-81-9	Rats:Wistar Han Mice:B6C3F1	Gavage	2 years	Dunnick
Perfluorooctanoic acid	335-67-1	Rats:Harlan Sprague Dawley	Feed	2 years	Blystone
Resveratrol	501-36-0	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Gavage	2 years	Germolec
Sodium tungstate, dihydrate	10213-10-2	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Drinking water	2 years	Behl
Tetrabromobisphenol A	79-94-7	Rats:Wistar Han Mice:B6C3F1/N	Gavage	2 years	Dunnick
Triclosan	3380-34-5	Mice:B6C3F1/N	Dermal	2 years	Fang
Trim VX (metal working fluid)	N/A	Rats:Wistar Han Mice:B6C3F1/N	Inhalation	2 years	Morgan
Tris(2-chloroisopropyl) phosphate	13674-84-5	Rats:Harlan Sprague Dawley Mice:B6C3F1/N	Feed	2 years	Stout
Vinylidene chloride	75-35-4	Rats:F344/N Mice:B6C3F1	Inhalation	2 years	Wyde
Zinc carbonate, basic	5263-02-5	Rats:Harlan Sprague Dawley	Feed	2 years	Wyde

Table 19. Chronic Toxicity/Carcinogenicity Studies Initiated During FY 2013

Study	CASRN	Species/Strain	Study Route	Length	Study Scientist
Triclosan	3380-34-5	Mice:B6C3F1/N	Dermal	2 years	Fang

v. Toxicogenomic Studies

NTP is working to bring the latest toxicogenomics technology into its testing program, to help revolutionize the way studies are conducted. Toxicogenomics examines how the entire genetic structure, or genome, is involved in an organism's response to environmental toxicants. Microarray, next-generation (NextGen) sequencing, proteomics, and metabolomics are among the advanced technologies that NTP is using to study the way chemical exposures change the expression of genes, proteins, and metabolites in critical cells and tissues. Measuring genome-wide changes in affected tissues may be useful for identifying biomarkers of disease and exposure to toxic substances, and for understanding individual genetic susceptibilities. Biomarkers that can be found in easily obtainable samples, such as blood and urine, could then be monitored in clinical studies. When biomarkers are validated, they can be repeatedly sampled during long-term NTP studies, to determine whether chemical exposures can be detected, or whether developing cancers provide a genetic signature.

NTP is interested in determining if analyzing the patterns of gene expression can provide indicators of toxicity at earlier time points and at lower doses than possible with traditional toxicology parameters. Evaluating patterns of gene expression may provide more than a link between genetics and morphology, because it is expected to provide insights into the pathogenesis of the disease and how different rodent models respond to toxicants. Some of the FY 2013 toxicogenomic studies involved NextGen sequencing technologies that bring gene expression to a base-pair resolution of accuracy and increased sensitivity. In addition, metabolomics represents a promising area of study, as it can elucidate how chemicals affect metabolism within cells, relative to changes in gene expression.

NTP is currently evaluating study conditions that may contribute to differential gene expression, such as animal and tissue variability; identifying best methods for tissue sampling; and establishing standards for conducting toxicogenomic studies under laboratory conditions. Planned or ongoing NTP toxicogenomic studies are listed in **Table 20**. More information can be found at *http://ntp.niehs.nih.gov/go/20358*.

Table 20. Toxicogenomic Studies Planned or Ongoing

Chemical	CASRN	Species/ Strain/ Cell Line	Study Route	Study Length/Test Type (Platform)	Study Scientist
Aflatoxin B1	1162-65-8	Rats:F344/N	Feed	90 days/Toxicity NextGen sequencing RNAseq (Illumina)	Merrick
Arsenite	7784-46-5	Human:Prostate (RWPE-1 cells)	Cell culture	30 weeks/NextGen sequencing DNAseq RNAseq (Illumina)	Merrick
Black cohosh	84776-26-1	Mice:B6C3F1/N	Gavage	90 days/Toxicity Microarray (Affymetrix)	Cora
tert-Butylphenyl diphenyl phosphate	56803-37-3	Rats:Harlan Sprague Dawley	Gavage	90 days/Toxicity Microarray (Affymetrix)	Auerbach
2,3-Dibromo-7,8-dichlorodibenzo-*p*-dioxin	50585-40-5	Mice:B6C3F1	Gavage	3 days/Immunotoxicity PCR-Array	DeVito
N,N-Dimethyl-*p*-toluidine	99-97-8	Rats:F344/N	Gavage	5 days, 90 days/Toxicity Microarray (Affymetrix)	Dunnick
Dong quai (*Angelica sinensis*) root extract	299184-76-2	Mice:B6C3F1/N	Gavage	90 days/Toxicity Microarray (Affymetrix)	McIntyre
Estrous cycle study in corn oil controls	8001-30-7	Rats:Wistar Han	Gavage	90 days/Microarray (Affymetrix)	Merrick
2-Ethylhexyl diphenyl phosphate	1241-94-7	Rats:Harlan Sprague Dawley	Gavage	5 days/Microarray (Affymetrix)	Auerbach
2-Hydroxy-4-methoxybenzophenone	131-57-7	Rats:Harlan Sprague Dawley	Feed	90 days/Toxicity Microarray (Affymetrix)	Auerbach

Chemical	CASRN	Species/ Strain/ Cell Line	Study Route	Study Length/Test Type (Platform)	Study Scientist
Isodecyl diphenyl phosphate	29761-21-5	Rats:Harlan Sprague Dawley	Gavage	90 days/Toxicity Microarray (Affymetrix)	Auerbach
Isopropylated phenol phosphate	68937-41-7	Rats:Harlan Sprague Dawley	Gavage	90 days/Toxicity Microarray (Affymetrix)	Auerbach
1,2,3,7,8-Pentabromodibenzofuran	107555-93-1	Mice:B6C3F1	Gavage	3 days/Immunotoxicity PCR-Array	DeVito
2,2',4,4',5-Pentabromodiphenyl ethers	5436-43-1	Rats:Wistar Han Mice:B6C3F1	Gavage	GD 6 through 3 weeks/ Toxicity Microarray (Affymetrix)	Dunnick
Pentabromodiphenyl oxide (technical) (DE 71)	32534-81-9	Rats:Wistar Han	Gavage	GD 6 to PND 21/Toxicity Microarray (Affymetrix)	Dunnick
3,3,4,4,5-Pentachlorobiphenyl	57465-28-8	Rats:Wistar Han	Gavage	GD 6 to PND 21/Toxicity Microarray (Affymetrix)	Dunnick
Pentachlorodibenzofuran	57117-41-6	Mice:B6C3F1	Gavage	3 days/Immunotoxicity PCR-Array	DeVito
2,3,4,7,8-Pentachlorodibenzofuran	57117-31-4	Mice:B6C3F1	Gavage	3 days/Immunotoxicity PCR-Array	DeVito
Phenobarbital	50-06-6	Rats:Wistar Han	Gavage	GD 6 to PND 21/Toxicity Microarray (Affymetrix)	Dunnick
Tetrabromobisphenol A	79-94-7	Rats:Wistar Han	Gavage	90 days/Toxicity Microarray (uterus and liver) (Affymetrix)	Dunnick/ Merrick
2,3,7,8-Tetrabromodibenzofuran	67733-57-7	Mice:B6C3F1	Gavage	3 days/Immunotoxicity PCR-Array	DeVito
2,2'4,4'-Tetrabromodiphenyl ether (DE-47)	5436-43-1	Rats:Wistar Han	Gavage	GD 6 to PND 21/Toxicity Microarray (Affymetrix)	Dunnick
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	1746-01-6	Mice:B6C3F1	Gavage	3 days/Immunotoxicity PCR-Array	DeVito
2,3,7,8-Tetrachlorodibenzofuran	51207-31-9	Mice:B6C3F1	Gavage	3 days/Immunotoxicity PCR-Array	DeVito
p-Toluidine	106-49-0	Rats:F344/NTac	Gavage	5 days, 90 days/Toxicity Microarray (Affymetrix)	Dunnick
2,3,7-Tribromodibenzo-*p*-dioxin	51974-40-4	Mice:B6C3F1	Gavage	3 days/Immunotoxicity PCR-Array	DeVito
Tricresyl phosphate	1330-78-5	Rats:Harlan Sprague Dawley	Gavage	5 days /Microarray (Affymetrix)	Auerbach/ Behl
Triphenyl phosphate	115-86-6	Rats:Harlan Sprague Dawley	Gavage	5 days/Microarray (Affymetrix)	Auerbach/ Behl

vi. Project Review Committee Approved

Table 21 lists studies that have been approved by either the internal NIEHS/NTP protocol approval committee or the internal NIEHS/NTP project review committee, but have not yet started during FY 2013.

Table 21. Protocol Approval Committee or Project Review Committee Approved Studies in FY 2013

Study	CASRN	Species/Strain	Study Route	Test Type/Study Length	Study Scientist
N,N-Dimethyl-*p*-toluidine	99-97-8	Rats:F344/NTac Mice:B6C3F1/N	Gavage	Microarray/5 days, 13 weeks	Morgan
Black cohosh	84776-26-1	Mice:B6C3F1/N	Gavage	Evaluation of subchronic macrocytic mon-regenerative anemia	Blystone/ Cora
Black cohosh	84776-26-1	Mice:B6C3F1/N	Gavage	Toxicogenomic changes associated with subchronic macrocytic non-regenerative anemia	Blystone/ Cora
Parabens: Butylparaben Ethylhexylparaben Hexylparaben Nonylparaben Propylparaben	 94-26-8 5153-25-3 1083-27-8 38713-56-3 94-13-3	Rats:Harlan Sprague Dawley	Gavage	Estrogenic activity (uterotrophic) and liver toxicity signature	Blystone
p-Toluidine	106-49-0	Rats:F344/NTac	Gavage	Microarray/5 days	Morgan
trans-Resveratrol	501-36-0	Rats:Harlan Sprague Dawley	Gavage	Modified one generation	Germolec
Valerian (*V. officinalis*)	N/A	Rats:Harlan Sprague Dawley	Gavage	Prechronic toxicity Perinatal dose-range finding	DeVito

C. NTP Research

In addition to testing activities, a variety of NTP research projects are underway at NIEHS, NCTR, and NIOSH. The following NIEHS and NIEHS/NTP branches are actively involved in NTP research activities: Biomolecular Screening Branch, led by Raymond Tice, Ph.D.; Cellular and Molecular Pathology Branch, led by Robert Sills, D.V.M., Ph.D.; NTP Laboratory, led by Mike Waalkes, Ph.D.; Program Operations Branch, led by Michelle Hooth, Ph.D.; and Toxicology Branch, led by Paul Foster, Ph.D.

The NTP Laboratory, within NIEHS/NTP, conducts in-house, agent-specific, targeted research related to the development and application of modern toxicology and molecular biology tools. These tools are used in the evaluation of specific substances of concern to NTP, issues of central importance to NTP programs, and methods development to advance the NTP mission. The NTP Laboratory also focuses on the study of the developmental origins of adult diseases. **Table 22** includes projects in the NTP laboratory in FY 2013.

Table 22. NIEHS/NTP NTP Laboratory Projects in FY 2013	
NTP Labs Project [Study Scientist]	**Objective and/or Project Summary**
Development of in vitro models of metal carcinogenesis [Waalkes]	To develop in vitro cell transformation models with target relevant cells using arsenic and cadmium.
Epigenetics in malignant transformation [Waalkes, Thayer]	To assess the epigenome of a series of isogenic cell lines transformed by genotoxic or epigenetic carcinogens and perform gene specific methylation analyses.
Formaldehyde in p53 knockout mice [Morgan]	To define the role of formaldehyde inhalation and hematopoietic tumor induction.
Formaldehyde-induced transformation of human myeloid progenitor cells [Waalkes]	To perform a proof of concept study, in vitro formaldehyde induced malignant transformation in hematopoietic stem cells. Companion study to the p53 study mentioned above.
Indium-tin-oxide and indium compounds [Morgan]	To perform various in vivo inhalation or in vitro toxicity studies.
Japan arsenic poisoning human study; Developmental basis of human disease [Waalkes]	To determine the genomics of response to early life arsenic exposure in survivors of a baby food poisoning event in Japan in the mid-1950s from a population now getting excess cancer typical for arsenic exposure. Human proof of the developmental basis of adult disease.
"Metalloestrogens" and uterine/breast response [Dixon, Waalkes, Fenton]	To re-test the ability of reported "metalloestrogens" like cadmium and arsenic to cause estrogen receptor stimulation in the uterus as a mode of action towards cancer development.
Method for assessing biological impact of metal particle dissolution [Morgan, Waalkes]	(1) To develop in vitro trans-well method with metal particles and macrophages in one well and cells of interest (such as lung epithelium) in the other, and (2) to define ability of various types of macrophages to release different metals from different particles.
Methods in histopathology of mammary gland development [Fenton]	To develop standardized methods to quantitatively assess chemical insult to mammary gland development.
Refinement of developmental neurotoxicology methods [Harry]	To improve methods for various efforts including genetic signatures, stem cells, inflammation, behavior, and conditioning.
Role of microRNAs in malignant transformation [Waalkes]	To study genes of interest involved with the epigenetics of malignant transformation using in vitro human model systems of carcinogenesis. MicroRNAs are thought to be a key epigenetic or post-transcriptional gene express control mechanism.
Stem cells in toxicology and carcinogenesis [Waalkes]	To perform various in vitro studies on the role of stem cells and cancer stem cells in carcinogenesis and the developmental basis of adult disease.
Studies on estrogen receptor in vitro [Waalkes]	To study mammary cells and so called "metalloestrogens."
Toxicants and mammary gland development [Fenton]	To determine the effects of different toxicants, including atrazine, on mammary gland development in rats and mice.

Genetic and epigenetic differences between individuals in the human population are proposed to be the basis for individual susceptibility to environmental stressors. Environmental and drug safety assessments are currently conducted with a small number of commonly used animal models that have limited genetic diversity and are insufficient to evaluate the influence of individual genetic differences on chemical and drug toxicity. These models are of limited value in extrapolating results to human toxicity and disease, and this program works toward developing models that are more appropriate. The NTP Biomolecular Screening Branch conducts in-house projects aimed at understanding individual susceptibility.

Table 23. NIEHS/NTP Biomolecular Screening Branch Projects in FY 2013

Host Susceptibility Project [Study Scientist]	Objective and/or Project Summary
Mouse Methylome Project [Merrick/Wade]	Male and female C57BL/6N mice were crossed with C3H/HeN mice, and five tissues (brain, liver, cardiac and skeletal muscle, brown and white fat, epididymal sperm) from the first generation offspring were collected at the average age mice would start an NTP subchronic toxicity study and flash-frozen for DNA/RNA isolation and liver sequencing. Progress in FY 2013 involved completion of liver transcript expression levels, genomic DNA sequencing, and DNA methylation mapping after bisulfite sequencing of both parental strains and the resulting first generation offspring by high throughput sequencing technologies and intensive computational data analyses. A manuscript is in preparation to be followed by public release of the methylome data.

i. Assessing Exposure to Substances in the Workplace

In following its mandate to protect workers' health and safety, NIOSH carries out research projects for NTP, to assess the effects of exposure to substances through an interagency agreement with NIEHS (see **page 16**). Setting priorities in occupational toxicological research is based upon several sources of information that are developed and maintained by NIOSH. These include health hazard evaluations, industry-wide studies, gaps in knowledge identified while developing criteria for recommended standards or criteria documents, current intelligence bulletins, hazard reviews and alerts, other technical reports, and information profiles on chemical hazards. **Table 24** lists NIOSH/NTP projects in FY 2013.

Packing up the NIOSH mobile lab for a field study

Table 24. NIOSH/NTP Research Projects FY 2013	
NIOSH/NTP Projects [Project Officer]	**Objective and/or Summary**
Biomonitoring, Biomarker Development and Health Assessment	
Reproductive health assessment of male workers [Schrader]	To evaluate reproductive health hazards using a health profile consisting of biomarkers for assessing male fecundity. Current efforts will focus on completing the Longitudinal Investigation of Fertility and the Environment (LIFE) project, a collaborative effort between NIOSH and the NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development. This work includes development of new biomarkers to include in the male reproductive health profile.
Immunochemical biological monitoring for occupational exposure and disease [Striley]	To evaluate industrial chemicals with known acute and chronic toxicities, which present a significant exposure risk for workers. Biological monitoring can assess exposure by analyzing acute and latent metabolites in various biological media. The goal of this project is to develop low-cost, rapid immunochemical and analytical chemistry biomonitoring methods that will be used to identify exposures and evaluate potential interventions. Concurrent with development of exposure assessment methods, this project will identify and develop new multiplex immunochemical methods to evaluate biomarkers of occupational illness or subclinical signs of occupational illness. Biological monitoring, through the validation and development of new methods, is a powerful tool for reducing risk and creating safer work practices.
Ultraviolet native fluorescence-based monitor for workplace exposures [Snawder]	To develop and evaluate a readily adaptable, next generation, direct reading, personal monitors for use in measuring worker exposure to a wide variety of chemicals including naphthalene and components of asphalt fume. The development of personal monitors for volatile and semi-volatile workplace chemicals will be helpful in rapidly assessing chemical exposure and will result in more realistic occupational exposure assessments and allow for rapid interventions leading to reduced worker exposures and thus preventing occupational illness and disease.
Workplace exposure, inflammation, and cardiovascular toxicity [Erdely]	To investigate the role of ultrafine/nanoparticle-induced cardiopulmonary inflammation and to identify specific markers of lung inflammation that directly correlate to systemic effects. This laboratory-based research will evaluate novel molecular mechanisms involved in the link between occupational exposures to ultrafine/nanosize particulates and the development of cardiovascular diseases. Planned studies will help to identify potential risk factors, biomarkers, and specific targets for prevention and therapeutic intervention of occupational-related cardiovascular diseases.
Systematic assessment of multi-walled carbon nanotubes in pulmonary disease [Qian]	To detect and identify novel biomarkers and molecular mechanisms of multi-walled carbon nanotube-induced pulmonary diseases, including fibrosis and cancer, for early detection and treatment interventions. Concerns over potential adverse pulmonary effects of airborne exposure to multi-walled carbon nanotubes have been raised due to their high aspect ratio (length/diameter), nanoscale diameter, fiber like-shape, durability and biopersistence. Increasing evidence has indicated potential pulmonary health hazards associated with pulmonary exposure to multi-walled carbon nanotubes, including inflammation, damage, fibrosis, and potential carcinogenesis. Nevertheless, the mechanisms underlying these adverse multi-walled carbon nanotube-induced pulmonary responses are not well-understood. Currently, there is no available non-invasive screening test for early detection of lung fibrosis.
Industry-wide studies of workers exposed to carbon nanotubes and nanofibers [Schubauer-Berigan]	To collect exposure data from participating pilot-scale or full-scale manufacturers or users of single-walled or multi-walled carbon nanotubes and carbon nanofibers. A study of biomarkers of early pulmonary, cardiovascular, and carcinogenic effect will be carried out among workers at these facilities.

NIOSH/NTP Projects [Project Officer]	Objective and/or Summary
Mortality, cancer incidence and biomarker studies [Ruder]	To elucidate exposure-outcome associations, especially dose-response relations, for risk assessment and to examine relationships between biomarkers (of exposure, susceptibility, and oncogene expression) and health effects.
Environmental Monitoring	
Analytical research and development infrastructure [Streicher]	To provide for the administrative needs and analytical instrumentation repair and maintenance in support of Chemical Exposure and Monitoring Branch chemists conducting research on sampling and analytical methods development for workplace chemicals. New methods needed to assess chemicals being investigated as part of the NIOSH/NTP exposure assessment interagency agreement are developed in this project.
Diacetyl exposure assessment [Streicher]	To develop and evaluate sampling and analytical methods for diacetyl and other flavoring compounds to enable accurate exposure assessment and evaluation of the effectiveness of control technology. Two sampling and analytical methods are being investigated for measurement of specific flavoring compounds, most notably diacetyl and 2,3-pentanedione in airborne particles and bulk powders. Finally, broader gas chromatography-mass spectrometry method(s) will be developed for a range of compounds present in flavorings.
Chemical exposure monitoring with indoor positioning [Brown]	To investigate a direct reading exposure method that uses a personal photo ionization detector chemical monitor with telemetry and an indoor positioning system to provide remote monitoring of a worker's exposure to volatile organic chemical (VOC)s with position and time. The personal monitor continuously samples and analyzes the workers breathing zone air for VOCs while recording their position and time of exposure. Indoor positioning is accomplished using a radio transmitter attached to the personal monitor and receivers place in the ceiling corners of the room. The positioning receivers communicate with each other and a remote laptop using wireless local area network technology. The remote laptop calculates and visualizes the worker position and exposure level. Once developed, this technology will be applied to analyze workplace exposures to diacetyl.
Exposure Assessment	
Exposure assessment for toxicologically-important chemicals [Curwin]	To characterize workplace exposures to (1) welding fumes with emphasis on manganese, (2) indium and indium compounds, (3) diacetyl, (4) 2-methoxy-4-nitroaniline, and (5) 2',2'''-dithiobisbenzanilide. A new study will investigate worker exposures to BPA. These chemicals have been nominated by various groups to the NTP. We will identify possible candidate industries, labor unions, workplaces, and uses and users; determine if there is relevance for occupational health; estimate number of workers exposed; and perform limited workplace exposure sampling.
Industry-wide Studies Branch research, development, and planning [Whelan]	To support strategic planning and feasibility studies of high priority/emerging problems in occupational health.
Nanotechnology field evaluations [Geraci]	To obtain information from as many different facilities, as possible, in the field on the nature of engineered nanomaterials, the processes involved in their manufacture and use, potential worker exposures, and work practices and control procedures used where nanomaterials are produced or used. As toxicology studies identify the biologic hazards of nanomaterial, it is important to gain a better understanding of actual workplace exposures.

NIOSH/NTP Projects [Project Officer]	Objective and/or Summary
Immunotoxicity and Immunology	
Immunotoxicological evaluation of occupational chemicals [Anderson]	To identify occupational and environmental chemical hazards and evaluate immune function and mechanism associated with exposure. The Immunotoxicology and Hazard Identification Lab will achieve this goal through both individual projects and collaborations. This research will contribute to increased identification of immunological hazards encountered in the workplace. Further evaluation of these compounds will allow for better risk assessment which will ultimately establish occupational exposure limits.
Airway fungal exposure and allergic sensitization in mice [Green]	To compare the immunological health effects of lung exposure to fungal spores or to hyphal fragment preparations. Agriculture as well as construction and remediation workers are exposed to elevated levels of fungi and can experience rhinitis, respiratory allergic symptoms and/or asthma as a result of their exposure. This project has been completed and had two major areas of study: (1) to determine the health effects following aspiration of hyphal fragments from *Stachybotrys chartarum* and *Alternaria alternata* in the absence of intact spores in mice; and (2) to compare the ability of aspirated spores or hyphal suspensions from *Aspergillus* spp, *S. chartarum*, and *A. alternata* to exacerbate respiratory allergy to ovalbumin.
Identification of occupational allergens [Beezhold]	To identify exposures to substances that can cause inflammatory or immune reactions in certain work environments. These exposures are important causes of occupational lung diseases such as asthma and allergic alveolitis. This project is intended to address these concerns through the development of improved techniques for the detection of such immune reactions before adverse clinical outcomes occur, and through the development of improved techniques for the detection and identification of inciting occupational agents. The project will involve the analyses of clinical samples, environmental bulk samples, and environmental aerosol samples. Successful completion of these investigations should lead to the development of effective prevention strategies for occupational allergies and asthma.
Genetics	
Genetics in occupational diseases [Yucesoy]	To investigate susceptibility gene variants, which contribute to the development and severity of occupational irritant contact dermatitis and asthma, using high-density and high throughput genotyping platforms. Previous and on-going studies in our laboratory showed that cytokine polymorphisms have a major influence on silicosis, dementia, and accelerated decline in lung function and vaccine efficacy. Understanding the genetic contribution to the development, progression and outcomes of complex occupational diseases will help improve the accuracy of risk assessment and improve safe exposure levels for genetically susceptible groups in the workforce.
Genetic fingerprint of mouse lung cancer [Reynolds]	To determine if there are different carcinogen-specific chromosomal (genetic) markers in spontaneously-occurring and chemically-induced mouse lung adenocarcinomas using in vitro and in vivo animal models. Mice were exposed by inhalation to vanadium pentoxide, nickel oxide or cumene (a benzene derivative). Workers in the construction and manufacturing sectors are exposed to these compounds. We are also planning to analyze mouse lung tumors induced by single-wall carbon nanotubes. If these experiments are successful we plan to extend these findings to tumors from occupationally-exposed human populations. Results from these studies will be used to establish biomarkers for early detection and therapeutic intervention of lung cancer in worker populations.

ii. Comprehensive Assessment of Occupationally-Relevant Exposures

NIEHS is coordinating an NTP effort with NIOSH to better understand worker exposures, identify occupational health research gaps, and educate workers. The NIEHS-NIOSH interagency agreement supports these projects. Current efforts listed in **Table 25** address worker exposures to welding fumes, nanosized materials, food flavorings, bisphenol A, indium compounds, and other industrial chemicals.

Table 25. NIEHS-NIOSH Interagency Agreement on Occupationally Relevant Exposures in FY 2013

Study [Study Scientist]	Objective and/or Rationale
Administrative support [Whelan]	To enable NIOSH scientists to (1) participate in review and oversight of NTP activities and (2) attend NTP-related meetings in Research Triangle Park, NC and Washington, D.C.
Assess the feasibility of an occupational exposure assessment of welding fume with emphasis on manganese compounds [Hanley]	(1) To identify industries (such as construction, shipbuilding, railroad, and manufacturing), companies, and/or unions involved in welding operations where the potential for substantial manganese exposure exists, for exposure assessments; (2) to develop methods to identify specific manganese compounds, different valence states, and potential solubility contained within various welding fumes matrices; and (3) to characterize welding fume exposures based on welding-associated jobs, tasks, and processes.
Exposure assessment of diacetyl and other flavorings in food production industries [Curwin]	(1) To characterize workplace inhalation exposures to diacetyl in food production industries that use food flavorings, (2) to document high-exposure activities and processes in the flavored food production industries, (3) to identify work practices and procedures that affect exposure, (4) to document engineering controls, and (5) to field test novel techniques for both gravimetric and volatile sampling.
Assessment of use of indium and indium compounds in the workplace [Hines]	(1) To contact and visit companies to determine indium materials being used, jobs and processes with potential indium exposure, exposure controls, and indium use trends and (2) to conduct preliminary sampling for indium, if possible.
Exposure assessment of engineered nanoparticles [Geraci]	(1) To identify workplaces engaged in the synthesis, manufacture, and use of engineered nanomaterials and (2) to characterize workplace exposure to selected engineered nanoparticles.
Exposure assessment of 1-chloro-4-(trifluoromethyl) benzene (PCBTF) [Harper]	(1) To identify worker populations at elevated risk of inhalation and surface exposure to PCBTF during manufacturing processes, (2) to update a previously published analytical method for quantitatively assessing PCBTF airborne vapors and surface exposures to allow the use of capillary column chromatography, and (3) to characterize industry-wide occupational exposures, including total number of workers, and evaluate patterns of exposure to PCBTF.
Durability of nanoscale cellulose fibers in artificial human lung fluids [Stefaniak]	To investigate the in vitro durability of nanocellulose materials in artificial lung fluids. Data generated from this study will be used to inform larger and more costly in vivo inhalation studies.
Exposure characterization and reproductive health of men working with bisphenol A (BPA) in the United States [Hines]	(1) To determine BPA usage in industry, such as which industries and jobs use BPA and which tasks are associated with exposure; (2) to develop air and wipe sampling methods for BPA using liquid chromatography mass spectrometry and liquid chromatography with ultraviolet detection; (3) to assess exposure to BPA among workers in these industries through air, wipe, and urine sample collection. If worker exposures are confirmed (4) to assess the reproductive health of men exposed to BPA in the workplace, and (5) to determine if there is a relationship between occupational exposure to BPA and reproductive health.

Study [Study Scientist]	Objective and/or Rationale
Industry-wide exposure assessment study of workers exposed to carbon nanotubes and nanofibers [Dahm]	(1) To establish sampling and analysis protocols for detection and quantification of carbon nanotubes and nanofibers, (2) recruit companies and conduct exposure assessments for carbon nanotubes and nanofibers in a representative sample of United States workplaces, (3) document high exposure tasks and processes as well as collect full work shift, personal breathing zone samples, (4) refine exposure assessment methods which include lowering the detection limit for elemental carbon (NMAM 5040), and (5) evaluating higher-flow, respirable cyclones to assess health-relevant exposures.

iii. Immunotoxicology Research

The NIEHS-NIOSH interagency agreement provides support of NTP hazard identification activities, aimed at preventing diseases or adverse effects, caused by environmental exposure to chemical or physical agents. These cooperative studies continue to improve risk assessment, by measuring what constitutes an adverse health effect on the immune system in humans. The studies, listed in **Table 26**, evaluate unique cohorts of individuals from professions associated with immune-mediated occupational diseases.

Table 26. NIEHS-NIOSH Interagency Agreement on Immunotoxicology Studies in FY 2013

Study [Study Scientist]	Objective and/or Rationale
NIEHS agricultural pesticide study [Green]	To support the NIEHS Agricultural Health Study, screening of 1,454 farmers serum for total immunoglobulin E (IgE) and mold mix specific IgE using the Phadia Immunocap assay has been completed. Those farmers who were mold-mix-positive have recently been tested against a 10-mold-specific IgE panel (n = 126). This component of the study is finished and the compiled data has been forwarded to NIEHS. In further support of the NIEHS Agricultural Health Study, the laboratory has been requested to screen an additional 640 farmers' sera samples for total and specific IgEs. Total IgE and mold-mix-specific IgE will be determined using Phadia ImmunoCap assays as previously described. The data derived from this analysis will be sent to NIEHS and prepared for publication in an allergy journal.
A marker for *Aspergillus terreus* exposure [Green]	To develop new and improved methods for detecting fungal exposure. In this project the emerging opportunistic fungal pathogen, *Aspergillus terreus,* has been used as a model fungal species. Terrelysin, a cytolysin and potential biomarker of fungal infection, was characterized and a recombinant protein produced. The recombinant terrelysin was then used to immunize mice to produce terrelysin specific monoclonal antibodies. Seven specific monoclonal antibodies were produced and used to characterize the production of terrelysin. Monoclonal antibodies binding sites are currently being determined in epitope mapping experiments. Several manuscripts have been recently published that report these findings. The development of a sensitive immunoassay that can be used in the serological detection of this biomarker is anticipated.
Animal model for airway exposure to dry fungal aerosols [Green]	To develop a murine model of dry fungal exposure to better mimic natural human exposures to fungi. In collaboration with aerosol scientists at NIOSH, an acoustical generation system has been developed. In preliminary experiments, histopathology and bronchoalveolar lavage fluid analysis demonstrated pulmonary deposition of conidia following dry fungal bioaerosol exposure. The system has been optimized for the generation of fungal spores. Once the system has been fully characterized, experiments are planned to further characterize the immune responses associated with various fungal species that frequently colonize water-damaged buildings or are occupationally relevant.

Study [Study Scientist]	Objective and/or Rationale
Characterization of fungal diversity in the indoor built environment [Green]	To investigate and characterize the diversity of fungal bioaerosols in the indoor built environment using large-scale ribosomal RNA sequencing in collaboration with the Kansas City Safe and Healthy Homes Partnership Project. In preliminary studies, various methods of extraction were compared and tested on occupational dust samples. A standardized extraction method was then used on 30 air and dust samples derived from homes participating in the project. Results from this analysis have been compiled and provide detailed insight into the diversity of previously overlooked fungal bioaerosol sources in the Kansas City Environment. Future studies in collaboration with Assured Bio, Inc., are planned for 2013. These studies aim to further evaluate indoor environments using large scale ribosomal RNA approaches from samples collected in contaminated and non-contaminated Atlanta, Georgia, homes. In addition, fungal species richness identified in this analysis will be directly compared to commercially available methods of fungal analysis including the Environmental Relative Mold Index.
The role of genetic variation in environmental and occupational diseases: irritant contact dermatitis [Yucesoy]	(1) To investigate whether the 24-hour irritant patch test is predictive of occupational hand dermatitis caused by high exposure to hand washing in health care workers, and (2) to investigate association between genetic variations in specific candidate genes (with emphasis on variants of cytokines, major histocompatibility complex region, antioxidant enzyme genes and genes related to skin barrier integrity) and irritation threshold levels of the subjects with development of irritant contact dermatitis. This study is in collaboration with Case Western Reserve and West Virginia Universities.
The role of genetic variation in environmental and occupational diseases: allergic contact dermatitis [Yucesoy]	(1) To investigate genetic factors in individuals predisposed to develop allergic contact dermatitis, specifically induced by nickel and (2) to investigate genetic factors involved in the development of allergic contact dermatitis in individuals sensitized to weak allergens, individuals sensitized to allergens that require metabolism in the skin, and individuals who react to more than three allergens of the standard screening series. This study is in collaboration with Case Western Reserve University and Dartmouth-Hitchcock Medical Center.
The role of genetic variation in environmental and occupational diseases: occupational asthma [Yucesoy]	(1) To investigate whether genetic variations in specific candidate genes (such as cytokine, major histocompatibility complex region, antioxidant enzyme genes) are associated with asthma induced by diisocyanates, and (2) to investigate potential associations between genetic variations in candidate genes and occupational asthma caused by low molecular weight agents. This project is in collaboration with the Universities of Montreal and Cincinnati.
The role of genetic variation in environmental and occupational diseases: chronic beryllium disease [Yucesoy]	To investigate the contribution of genetic variations in the major histocompatibility complex region to the development of beryllium sensitization and chronic beryllium disease. This study is in collaboration with National Jewish Medical and Research Center.
Investigations into health effects caused by exposure to indoor air reaction products (supportive animal studies) [Wells, Anderson]	(1) To identify and measure the reaction products of gas-phase compounds present in the indoor environment, especially oxygenated organics; (2) to further develop and validate a novel in vitro exposure methods utilizing realistic indoor chemistry scenarios to expose cells and tissues to these indoor air reaction products; (3) to complete both in vitro and in vivo assays to assess adverse health effects caused by indoor air reaction products; and (4) to further investigate the role of structurally similar indoor air chemicals present in mixtures in the indoor environment.
Alternative methods for chemical allergen identification and assessment: use of immunochemical techniques for investigation of diisocyanate allergic diseases [Siegel]	(1) To develop an amine based probe for kinetic assessment of chemical binding (haptenation) that will complement the thiol based probe previously reported by our laboratory, (2) to assess potential for inclusion of a metabolic activation step in our kinetic based assays for identification of prohaptens, (3) to expand the compilation of chemical allergens assessed by kinetic electrophilic reactivity analyses for comparison to reported allergenic potencies (murine local lymph node assay exposure concentration values), and (4) to use in-house developed monoclonal antibodies against diisocyanate bound proteins to identify potential haptenation targets.

Study [Study Scientist]	Objective and/or Rationale
Analysis of mycotoxins in dust samples from a water-damaged building [Park]	(1) To develop a cost-effective method using a state-of-the art technology, ultra-performance liquid chromatography-tandem mass spectrometry, for simultaneously analyzing multiple fungal toxins in environmental samples, and (2) to perform experiments to examine stability of the mycotoxins in floor dust stored in different temperature conditions at different points of time using the developed method. The developed method will be applied to quantify fungal toxins in floor dust samples that will be collected from a funded school study in 2014, and samples previously collected from water damaged buildings for which we have existing data on fungal and bacterial components as well as occupants' health. The ultra-performance liquid chromatography-tandem mass spectrometry technology does not require significant sample preparation, and thus the technology enables us to develop rapid and robust methods to screen multiple mycotoxins in samples. The project provides us with an opportunity to examine potential roles of exposure to fungal toxins on occupants' health in water-damaged buildings.

iv. NTP Research in Partnership with NCTR

NCTR, in partnership with researchers from elsewhere in FDA, other government agencies, academia, and industry, provides innovative technology, methods development, vital scientific training, and technical expertise. The unique scientific expertise of NCTR is critical in supporting FDA product centers and their regulatory roles. These NCTR-NTP studies, funded by NCTR voluntary allocations, are listed in **Table 27**. **Table 28** lists projects that are funded through FDA and NTP interagency agreements.

Table 27. NCTR/NTP Projects in FY 2013

NCTR/NTP Project [Study Scientist]	Objective and/or Project Summary
Biochemical and Molecular Basis of Toxicology	
Biological based dose-response modeling for the thyroid axis in the fetus and neonate [Fisher]	(1) To create biological based dose-response models for the hypothalamic-pituitary-thyroid axis in the developing rat and human as a function of iodide status, (2) to interface the these models with physiologically-based pharmacokinetic or toxicokinetic models for thyroid active chemicals to predicted conditions (iodide status and chemical exposure) for which brain thyroid hormone homeostasis cannot be maintained in the fetus and neonate, and (3) to use the models to evaluate the possible influence of population exposures to thyroid active chemicals on fetal and neonatal thyroid status as a function of iodide intake.
Relationship between liver epigenetic phenotype and susceptibility to nonalcoholic steatohepatitis-induced hepatocarcinogenesis in mice [Pogribny]	(1) To determine the role of epigenetic dysregulation in the etiology and pathogenesis of dietary nonalcoholic steatohepatitis-induced hepatocarcinogenesis in mice, (2) to determine whether or not interstrain-specific susceptibility of mice to nonalcoholic steatohepatitis-induced hepatocarcinogenesis is associated with differences in individual hepatic epigenetic phenotypes, (3) to determine the role of epigenetic dysregulation in the etiology and pathogenesis of nonalcoholic steatohepatitis-induced hepatocarcinogenesis in mice induced by tamoxifen administration, and (4) to determine whether or not aberrant epigenetic markers can be used as targets for prevention of nonalcoholic steatohepatitis-induced hepatocarcinogenesis in mice.

NCTR/NTP Project [Study Scientist]	Objective and/or Project Summary
The role of ATP binding cassette-drug transporters in chemoresistance in pancreatic cancer [Pang]	(1) To compare various ATP binding cassette transporters' expression in normal and pancreatic adenocarcinoma specimens and to determine whether the expression of ATP binding cassette transporters is correlated with clinical aggressiveness of the tumor, (2) to evaluate whether the single nucleotide polymorphisms in ATP binding cassette transporter genes are associated with the abnormal expression of the efflux pumps and drug sensitivity, and (3) to assess the epigenetic regulation of ATP binding cassette transporters in pancreatic cancer.
Mechanism of tumorigenic pyrrolizidine alkaloids and development of liquid chromatography-electrospray ionization/multi-stage mass spectrometry (LC/ESI/MS/MS) methodology for detection and quantification of pyrrolizidine alkaloids [Fu]	(1) To validate the proposed mechanism by which pyrrolizidine alkaloids induce tumors in rodents, (2) to develop an LC/ESI/MS/MS method for detection and quantification of dehaloperoxidase-derived DNA adducts in rodents, (3) to develop an LC/ESI/MS/MS method for detection and quantification of Genotoxic pyrrolizidine alkaloids in herbal plants and herbal dietary supplements, and (4) to develop an LC/ESI/MS/MS method for detection and quantification of dehaloperoxidase-derived hemoglobin adducts in rodents.
Sequencing Quality Control Project [Su]	To assess the technical performance of different next-generation sequencing technologies and various bioinformatics strategies for handling and analyzing the massive sequence data sets by using the reference RNA samples previously established by the MicroArray Quality Control project and (2) to profile RNA samples isolated from cells with or without treatment by nanoparticles and toxicants of known mechanisms of toxicity to further evaluate their performance in assessing the safety and toxicity of FDA-regulated products by using next-generation sequencing technologies. Next-generation sequencing is expected to revolutionize transcriptome studies because of its claimed higher sensitivity and specificity, the capability of simultaneously detecting individual exons and alternative splicing, and the possibilities of genome-wide quantification (through single-molecule sequencing).This collaborative project is a natural extension of the FDA-led MicroArray Quality Control project.
Study of drug-induced liver toxicity using state-of-the-art in vitro liver models including primary rat and mouse hepatocytes and stem cells [Guo]	To obtain signature gene and protein expression patterns of each cell type for comparison to toxin-induced changes. In addition, the contribution of each cell type to overall liver toxicity from agent exposure can be determined once these isolated cell types are available reliably.
Dose-response genotoxicity of ethylmethane sulfonate in mice using the Pig-a and transgenic gpt delta assays [Cao]	(1) To use sensitive genotoxicity endpoints with low background frequencies to increase the sensitivity of the assays for detecting low-dose effects, (2) to measure genotoxicity using a design to detect the maximum responses, (3) to measure the effects of ethylmethane sulfonate exposure in neonatal as well as adult animals, and (4) to measure genotoxicity in the major target tissues for ethylmethane sulfonate carcinogenicity.
Neurotoxicology	
Evaluation and characterization of blood-brain barrier pathology in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-probenecid-induced Parkinson's disease-like conditions in a mouse model and its potential amelioration by endoplasmic reticulum stress reducers (molecular chaperones) and other putative anti-Parkinson therapeutics [Sarkar]	(1) To characterize and evaluate the role of key neurovascular elements such as pericytes, astrocytes, and endothelial cells and basement membrane proteins in the expression of Parkinson's disease-like pathology; and (2) to determine the ability of endoplasmic reticulum stress-reducers and related heat shock protein inhibitors to alter the expression of Parkinson's disease-like pathology and flavonoids (Mangiferin and Morin), antioxidants (N-acetyl cysteine and acetyl-l-carnitine), superoxide scavengers (such as tetramethylpyrazine), MAP kinase inhibitors (such as SB239063), synthetic dyes (Azure A and Thionin), and metal chelators (clioquinol and VK-28) to provide neuroprotection against Parkinson's disease-like pathology.

NCTR/NTP Project [Study Scientist]	Objective and/or Project Summary
Developing more complete genomic and histological evaluations of vascular damage in the brain meninges and choroid plexus after neurotoxic insult [Bowyer]	(1) To determine whether these two regions of meninges associated vasculatures differ with respect to gene expression, (2) to determine gene expression patterns present in the larger arteries compared to the arterioles and the meningeal layers (pia and some arachnoid membrane), (3) to evaluate the changes in meninges associated vasculatures during neonatal and juvenile periods, (4) to determine whether the gene expression profiles in the various components of meninges associated vasculatures respond differently to neurotoxic insults, and (5) to determine the possibilities of developing bioinformatic methods for predicting the relative genomic contributions of the various meninges associated vasculatures components (large arteries, arterioles, and meninges) to the overall genomic response of the entire meninges associated vasculatures under environmentally induced hyperthermia, amphetamine exposure, or control conditions.
Methods development for high-resolution dedicated positron emission tomography to rodent neuroplasticity and toxicity during development [Wang]	To use high-resolution dedicated positron emission tomograph to screen and evaluate in vitro and in vivo measurements from a broad range of pathophysiological or pharmacological parameters using specific tracers in the developing rat and three different age groups of developing rats (gestational day 18 female rats, post-natal day 7 rat pups, and post-natal day 35 rats).
Assessment of gaseous anesthetics in the developing nonhuman primate [Wang]	(1) To evaluate whether prolonged exposure to gaseous anesthetics nitrous oxide or isoflurane increases neuronal cell death, and to determine if combinations of nitrous oxide and isoflurane have additive effects in the developing nonhuman primate; (2) to determine if a relatively high dose or prolonged exposure of the developing nonhuman primates to nitrous oxide or isoflurane alone, or their combination will induce long-term behavioral deficits or pathological changes; (3) to determine the effectiveness of using noninvasive imaging techniques (high resolution dedicated positron emission tomography) and magnetic resonance imaging to monitor pathological changes in this model; and (4) to identify potential, underlying mechanisms that could link alteration of mitochondrial function and elevation of reactive oxygen species to gaseous anesthetic-induced neuronal cell death.
In vitro assay to predict developmental neurotoxicity of pediatric anesthetics [Wang]	To use rodent in vitro organotypic and primary culture models: (1) to examine the toxicity of anesthetics including propofol (gamma-amino butyric acid (GABA)-A agonist), baclofen (GABA-B agonist), diazepam (GABA-A agonist), pentobarbital (GABA-A agonist and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist), etomidate (GABA-A agonist), sevoflurane (N-methyl-D-aspartate antagonist and GABA agonist), fentanyl (opiate agonist) and anesthetic combinations commonly used in pediatric surgical procedures; (2) to determine the utility of in vitro culture systems to predict in vivo outcomes in subsequent studies; (3) to determine the dose and time-course over which the potential neurotoxic effects of anesthetics are expressed in the developing brain; (4) to determine effective ways to protect against anesthetic-induced developmental neurotoxicity that have potential clinical utility; (5) to identify mechanisms that link altered N-methyl-D-aspartate receptor function and/or elevation of reactive oxygen species to anesthetic-induced neuro-apoptosis; and (6) to identify biomarkers such as genomic pathway signatures and determine their validity for predicting in vitro outcomes of pediatric anesthetic exposure.
Methylphenidate (ritalin) exposure during pregnancy: assessment of neurotoxicity in offspring [Ferguson]	To determine the neurobehavioral toxicity associated with pre- and early postnatal treatment with methylphenidate in rats using a range of behaviors at preweaning, adolescent, and adult ages.

NCTR/NTP Project [Study Scientist]	Objective and/or Project Summary
Effect of pediatric anesthetics on zebrafish embryos: neurotoxicity verses gene expression changes and neuronal kinase cyclin-dependant kinase 5 as a mediator of toxicity [Kanungo]	(1) To determine whether ketamine has neurotoxic effects (on neurogenesis and axonogenesis) in zebrafish and (2) to determine if the window of such effects varies between early and late differentiating neurons (sensory and motor neurons, respectively).
Methods development for toxicity assays using the zebrafish embryo as a model system: whole animal high throughput assays for chemical testing [Kanungo]	(1) To use the established high throughput assay system using zebrafish embryos for morphological and behavioral endpoints of toxicity and subtle organ-specific toxicities to study the effect of methamphetamine on zebrafish embryos, especially relating to sensory and motor neuron development; (2) to determine if carbon nanotubes pass through the blood brain barrier in zebrafish embryos, and if so, do these nanomaterials generate reactive oxygen species, deplete dopamine and its metabolites (dihydroxyphenylacetic acid and homovanillic acid), and alter markers of oxidative stress; and (3) to determine the effect of nicotine on zebrafish embryos, especially relating to sensory and motor neuron development and the mechanism of action.
Long-term consequences of neonatal ketamine anesthesia in rhesus monkeys: extended cognitive assessments [Paule]	(1) To continue monitoring the cognitive capabilities of rhesus monkey subjects that were exposed to a single, 24-hour duration of ketamine-induced anesthesia during the first week postpartum; and (2) to extend the functional domains that are being assessed beyond learning, the ability to perform simple visual discriminations, motivation, and speed of psychomotor processing, to include performance of a temporal discrimination task (timing task), a counting task, and reversal learning tasks (cognitive flexibility).
Development of a small, voxel, short echo time 1H magnetic resonance spectroscopy toolbox for biomarkers of neurotoxicity in rats [Liachenko]	(1) To establish a preclinical 1H-magnetic resonance spectroscopy platform toolbox for sensitive and fast measurements in small voxels and (2) to characterize acute effects of psychomodulators (amphetamine, ketamine) in normal rats using 1H-magnetic resonance spectroscopy S (preclinical biomarker development).
Nanotoxicology	
Antimicrobial properties of zinc oxide and titanium dioxide nanoparticles against multidrug-resistant *Staphylococcus* and *Enterococcus* spp. and their cytotoxic and genotoxic potential in bacteria and normal human epidermal keratinocytes and primary intestinal cells [Khan]	(1) To study the mechanism of antimicrobial properties of titanium dioxide and zinc oxide nanoparticles in multidrug-resistant *Staphylococcus* and *Enterococcus spp.*, (2) to study synergy between nanoparticles and antibiotics, (3) to evaluate the cytotoxic and genotoxic potential of nanoparticles in bacterial and normal human epidermal keratinocytes and primary intestinal cell lines, and (4) to study the transcriptomic gene expression in normal human epidermal keratinocytes and intestinal cell lines.
Immunological effects of nanoparticles on induction of pro-inflammatory responses to *Candida albicans* by vaginal epithelial cells [Wagner]	(1) To measure the effects of graphene and poly(lactic-co-glycolic acid) nanoparticles on messenger RNA and protein expression of inflammatory cytokines and signal transduction proteins by vaginal epithelial cells stimulated with *C. albicans* and (2) to measure oxidative effects and DNA damage in vaginal epithelial cells by nanoparticles.
Determination of cytotoxicity and genotoxicity of nanomaterials of interest to the FDA and mechanism of action [Fu]	To develop a set of cell-free and cell-based in vitro tests that can be used to rapidly identify nanomaterials of interest to the FDA that elicit oxidative damage and (2) to determine if in the presence of nano-metal materials, endogenous and dietary antioxidants can display pro-oxidative activity.

NCTR/NTP Project [Study Scientist]	Objective and/or Project Summary
Development of methods for determining nanoparticle penetration/ permeation into vaginal mucosal tissue [Zhang]	(1) To develop/adapt methods to deliver nanoscale material into rat vaginal tract and (2) to develop the analytical methods to quantify vaginal mucosal penetration of select nanomaterials following intravaginal lavage.
Neurotoxicity assessment of silver nanoparticles in PC-12 cells and in rats [Ali]	(1) To evaluate the neurotoxicity of different sizes of silver nanoparticles using cultured PC-12 cells; (2) to determine if in vitro exposure to silver nanoparticles selectively induces specific genomic changes in cultured PC-12 cells using microarrays; (3) to determine if single or multiple doses of silver nanoparticles produce reactive oxygen species, alterations in lipid peroxidation, or changes in antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase) or glutathione levels in the rat brain; (4) to determine if single or multiple doses of silver nanoparticles induce specific genomic changes (microarrays), neurotransmitter concentrations, or 3-nitrotyrosine formation in the rat brain; and (5) to determine if multiple doses of silver nanoparticles produce morphological alterations in blood-brain barrier, brain, or other visceral organs of the rat.
Evaluation of the applicability of in vivo micronucleus assays for assessing genotoxicity of engineered nanomaterials [Chen]	(1) To assess the genotoxicity of four types of nanoscale materials (carbon nanotubes, nanoscale titanium dioxide, nanoscale gold, and nanoscale silver) in three standard tests used for genotoxicity assessment by the FDA (*Salmonella* Ames test, mouse lymphoma assay, and in vivo mouse micronucleus assay); and (2) to evaluate the possible mechanisms of nanomaterial-induced genotoxicity using a transgenic mutation system, comet assay and genomic analysis.
Do engineered silver nanomaterials varying by size and coatings behave differently than bulk silver in their ability to induce genetic damage? [Chen]	To evaluate the genotoxicity of various sizes of engineered silver nanoparticles and bulk silver in the Ames test, mouse lymphoma assay, and in vitro micronucleus assay.
Assessment of iron oxide nanoparticle-induced neurotoxicity in cell cultures and whole animal models [Binienda]	To determine if acute or chronic exposure of different sizes of iron oxide nanoparticles produce: (1) specific changes in the mitochondrial function, cell death and generation of reactive oxygen species in different regions of rat and mice brain using in vivo microdialysis; (2) significant changes in neurotransmitter concentrations in different regions of mice/rat brains using microdialysis; (3) alterations in the brain free fatty acid levels; (4) alterations in lipid peroxidation and/or changes in antioxidant enzyme activity (catalase, superoxide dismutase, glutathione peroxidase) and glutathione levels in mice and rat brains; and (5) selective pattern of deposition and damage produces in different regions of rat and mice brain using in vivo magnetic resonance imaging.
Study of nanoparticles migration from food-contact nanomaterials: characterization and quantification of silver nanoparticles in stimulants [Trbojevich]	(1) To quantify the migration of nanoparticles from nanocomposites used in food-contact material and (2) to characterize and quantify silver nanoparticles in food stimulants.
Development and evaluation of exposure dosimetry methods to optimize the standard in vitro mammalian genotoxicity assays for assessing engineered nanomaterials [Chen]	(1) To evaluate whether the in vitro mammalian genotoxicity assay is suitable for assessing the genotoxicity of nanomaterials, (2) to explore the possible mechanisms underlying genotoxicity of engineered nanomaterials by conducting genomic analysis, (3) to identify potential improvements to the assay and general strategies for evaluating nanomaterials, and (4) to examine whether the suitable methods and other experiences learned from the micronucleus assay are applicable to other genotoxicity tests, such as mouse lymphoma assay and in vivo micronucleus assay.

NCTR/NTP Project [Study Scientist]	Objective and/or Project Summary
Assessment of size and shape dependent-toxicity of silver nanoparticles as measured by changes in the permeability at the gastrointestinal surface [Khare]	To investigate various cellular components involved in the uptake of nanoparticles in intestine, their accumulation in various cell types and the effect of nanoparticles on the intestinal microbiome, by: (1) determining the effect of nanomaterials on the permeability of intestinal epithelial cells in vitro and ileal mucosa ex vivo and (2) measuring the toxicity of silver nanoparticles as measured by changes in the expression of genes involved in the epithelial integrity of polarized epithelial cells and ileal mucosa.
Bioassay and Biomarker Development and Evaluation	
Biomarkers of liver toxicity [Mendrick]	(1) To discover biomarkers of hepatotoxicity in preclinical studies, which are predictive of adverse effects in humans, for eventual evaluation of predictivity in rodent assays (preclinical studies); and (2) to qualify the discovered biomarkers.
Phosphatidylinositol glycan complementation group A (Pig-A) mutagenesis: an international validation study comparing Pig-A mutation in rats with other biomarkers of genetic toxicity [Heflich]	(1) To generate data using a standardized protocol that, in combination with results from other investigators, will be used to determine the sensitivity, specificity, and portability of the rat red blood cell/reticulocyte Pig-A gene mutation assay; and (2) to compare the Pig-A assay results with the in vivo Comet and micronucleus formation assays, and hypoxanthine-guanine phosphoribosyltransferase lymphocyte gene mutation assays.
Development of predictive mitochondrial biomarkers for drug-induced cardiotoxicity using a system biology approach [Desai]	(1) To determine doxirubicin-induced changes in plasma troponin T, creatinine kinase-MB, and cardiolipin levels in rats, and to correlate with non-invasive measurements of heart rate, heart rate variability, and electrocardiogram; (2) to determine morphological changes in cardiac mitochondria in left ventricular region by electron microscopy; (3) to quantify analyte profiling in the heart using transcriptional profiling of approximately 906 mitochondria-related genes using MitoChip (genomics); (4) to conduct protein profiling by 2D-high performance liquid chromatography/tandem mass spectrometry (proteomics); and (5) to measure endogenous metabolites (creatinine, creatine, lactate, Krebs cycle intermediates, small ketone bodies in plasma) by nuclear magnetic resonance imaging and mass spectrometry (metabolomics).
Development of methods for evaluating DNA damage using single cell gel electrophoresis (comet assay) in rodents [Manjanatha]	To evaluate and establish methods and conditions that enhances the sensitivity and reproducibility of the in vivo alkaline-comet assay for use in preclinical-hazard identification and genotoxicity testing of food ingredients and chemicals for regulatory purposes.
Development and application of a mitochondria-specific gene array (Mitochip) for the investigation of pre-clinical and clinical predictive biomarkers of toxicity [Desai]	(1) To develop MitoChip for various mammalian species, including rat, non-human primate, and human; (2) to investigate the mechanisms of drug toxicities and degenerative diseases associated with mitochondrial dysfunction in different mammalian species by conducting transcriptional profiling of mitochondria-related genes; and (3) to characterize species-specific transcriptional profiles to predict risk of drug toxicity or disease onset in different mammalian species.
Further evaluation of the types of genetic events detected by the mouse lymphoma assay and the role of the assay in mechanistically based risk assessment [Moore]	(1) To determine if the L5178Y TK+/- mouse lymphoma assay adequately detects both aneuploidy and mitotic recombination, (2) to determine if L5178Y mouse lymphoma cells have active recombinase functions that lead to a large proportion of mutants that result from recombinase-mediated rearrangements, and (3) to determine the fundamental genetic mechanism(s) causing the small and large colony thymidine kinase mutant phenotypes.

NCTR/NTP Project [Study Scientist]	Objective and/or Project Summary
Validation of recently established gpt-delta mice at NCTR [Manjanatha]	(1) To dose gpt-delta transgenic mice with low, intermediate, or high doses of cyclophosphamide and bleomycin and 100 mg/kg ethylnitrosourea (cumulative dose) as a positive controls for induction of mutations in the transgenes gpt, red and gam genes (spi- selection); (2) to characterize recovered mutants from target tissues for generation of gpt and spi mutational spectra; and (3) to analyze red blood cells for phosphatidylinositol glycan complementation group A (Pig-A) mutant frequencies and erythrocytes for micronucleus frequencies.
Cancer mutations as biomarkers of cancer risk: human studies with implications for personalized medicine [Parsons]	(1) To develop the information necessary for the rational use of oncogene mutations as quantitative biomarkers of cancer risk; specifically allele-specific competitive blocker polymerase chain reaction will be used to determine normal and pathological levels of relevant oncogene mutations in multiple human tissues and tumors, (2) to compare the information derived from human tissues with data generated in a parallel rodent protocol as an approach for incorporating carcinogenesis-relevant data into the rodent for human extrapolation necessary in cancer risk assessment, (3) to validate a streamlined allele-specific competitive blocker polymerase chain reaction methodology and develop the methodology necessary to measure oncogene mutation frequency in cell-free DNA isolated from plasma, and (4) to communicate to the regulatory risk-assessment community the regulatory significance of data on tumor-associated mutations in rodents and humans.
Development of a new safety evaluation method using microRNA expression analysis as a biomarker for detecting carcinogens [Chen]	(1) To determine microRNA expression profiles of the tumor target tissues of rats and mice treated with the genotoxic carcinogens: aristolochic acid, riddelliine and comfrey, and the non-genotoxic carcinogens: propiconazole and triadimeforn, and the non-carcinogen myclobutanil using microarray technologies; (2) to develop a polymerase chain reaction array containing the primers, which are specifically used to amplify carcinogensis-related microRNAs, and to use the polymerase chain reaction array to conduct time-course and dose-response studies for microRNA expression alterations in tissues of rats treated with carcinogens; and (3) to define the microRNA biomarker genes that are associated with carcinogen exposure by predicting their target genes and determining their biological functions.
QT interval correction via mixed-effects modeling [George]	To develop an appropriate non-linear mixed effects pharmacokinetic model in order to examine the effects of bitter orange/synephrine extract on electrocardiogram data from a rodent study. QT interval is a measure of time in the heart's electrical cycle.
Establishment of embryonic stem cells as an in vitro model to explore developmental toxicity [Inselman]	(1) To develop an in vitro culture system utilizing mouse mesodermal embryonic stem cells and human pluripotent stem cells, and (2) to examine the mechanisms(s) responsible for embryotoxicity associated with selected known or suspect embryotoxins that affect differentiation into osteoblasts.
Assessing acetaminophen-induced liver injury and the influence of dietary supplements: potential synergistic interactions [Shi]	Using a battery of dietary supplements: (1) to determine the dose-response toxicological effect in vivo in mice following repeated dosing with each dietary supplement in the absence and presence of acetaminophen, and (2) where dietary supplements and acetaminophen administration resulted in greater hepatotoxicity, to examine the mechanism of action using genomics, proteomics, and metabolomics approaches for in vivo samples from mice and in vitro samples from primary hepatocyte cultures.
Effect of fetal exposure to oxybenzone on reproductive organs of postnatal day 21 rats [Nakamura]	To determine if fetal exposure to oxybenzone influences the male (testes, steroid biosynthesis) and female (ovary) reproductive organs of Harlan Sprague Dawley rats on postnatal day 21 by examining morphology of the reproductive organs and messenger RNA expression of genes related to the endocrine system.

NCTR/NTP Project [Study Scientist]	Objective and/or Project Summary
Effect of fetal or postnatal exposure to oxybenzone on reproduction in male rats [Nakamura]	(1) To evaluate the expression of genes involved in testosterone synthesis in testes and prostate of adult males treated with oxybenzone perinatally and as young adults, (2) to evaluate the expression of androgen-receptor genes in prostate and testes of rats treated with oxybenzone both perinatally and as young adults, and (3) to evaluate expression of DNA methyltransferase genes in the testes and prostate of rats treated with oxybenzone both perinatally and as young adults.
Evaluate the impact of Deepwater Horizon oil-contaminated Gulf seafood residues in edible tissues on the human intestinal microbiota of the consumer [Cerniglia]	(1) To determine whether polycyclic aromatic hydrocarbon residues in edible tissues of Deepwater Horizon oil-contaminated seafood adversely affect the human intestinal microbiota, (2) to determine if the human intestinal microbiota metabolize polycyclic aromatic hydrocarbons that are toxic components of Deepwater Horizon oil, and (3) to identify, characterize, and determine the toxicity of polycyclic aromatic hydrocarbon metabolites generated from degradation by human intestinal microbiota.
3D- and 4D- quantitative spectrometric data-activity relationship modeling applied to various toxicological endpoints [Beger]	(1) To develop 3D- and 4D-quantitative spectrometric data-activity relationship models for endocrine disruptors, lowest-observed-adverse-effects level and no observed-adverse-effects level, and other relevant toxicological endpoints; and (2) to determine how the technique used to predict 13C or 15N nuclear magnetic resonance spectra affects 3D-quantitative spectrometric data-activity relationship modeling.

Table 28. NIEHS-NCTR Interagency Agreement Studies in FY 2013

Study CASRN [Principal Investigator]	Objective and/or Rationale
AIDS Program	
Perinatal carcinogenicity of drug combinations used to prevent mother-to-child transmission of HIV *30516-87-1, 134678-17-4, 129618-40-2, 159989-65-8* [Beland]	To determine the carcinogenicity, genotoxicity, and metabolism of antiretroviral drug combinations administered to mice transplacentally and perinatally. Various combinations of the drugs AZT, lamivudine, mevirapine and Nelfinavir mesylate are being studied. The studies include 14-day range-finding and two-year chronic in pregnant C57BL6N females and in B6C3F1 hybrid offspring.
Dietary Supplements	
Thirteen-week studies to determine the pathogenesis of the whole leaf extract of the *Aloe vera* plant in the cecum and large intestine of the F344 rat *85507-69-3* [Boudreau]	To investigate the pathogenesis of *Aloe vera* extracts and gel, with and without added Aloin A, in the cecum and large intestine of the F344 rat. Senna, having similar components to those in *Aloe vera*, will also be studied to determine if it exerts comparable effects when administered in the drinking water of F344 rats.
Food Contaminants	
Assessment of molecular changes in male and female Sprague Dawley rats orally exposed to bisphenol A (BPA) from gestational day 6 through postnatal day 90 *80-05-7* [Camacho]	To determine BPA-induced molecular changes in gene expression, protein levels, and epigenetic modifications in tissues collected from Sprague Dawley rats orally exposed to BPA from gestational day 6 through postnatal day 90.

Study CASRN [Principal Investigator]	Objective and/or Rationale
Evaluation of toxicity of BPA in male and female Sprague Dawley (NCTR) rats exposed orally from gestational day 6 through postnatal day 90 *80-05-7* [Delclos]	(1) To assess the toxicity of BPA in rats dosed perinatally via gavage, and (2) to evaluate estrogenic endpoints from the first filial offspring generation.
Evaluation of various diets on endpoints critical to the evaluation of BPA and other endocrine-active agents [Delclos]	To evaluate reproductive and developmental endpoints in F0-F2 generation in CD-1 mice with various chows (such as Purina Mills 5K96, NIH-41, Purina Mills 5001), some of which have low isoflavone levels, in preparation of studies on BPA in CD-1 mice.
Two-year chronic toxicology study of BPA administered by gavage to Sprague Dawley (NCTR) rats from gestational day 6 until birth and directly to pups from postnatal day 1; continuous and stop-dose exposures *80-05-7* [Delclos]	To characterize the long-term toxicity of orally administered BPA, including developmental exposure, in the NCTR Sprague Dawley rat over a broad dose range. In addition, animals generated in this study will be assigned to separate protocols for assessment of a range of molecular, morphological, and functional endpoints to determine if these endpoints are predictive of long-term toxic effects or reveal potential effects undetected by standard toxicological evaluations.
Evaluation of molecular, morphological, and functional endpoints in Sprague Dawley (NCTR) rats treated with BPA administered by gavage from gestational day 6 until birth and directly to F1 pups from postnatal day 1; continuous and stop-dose (postnatal day 21) exposures *80-05-7* [Delclos]	To evaluate a range of molecular, morphological, and functional endpoints in rats dosed orally with a wide range of BPA doses in a chronic toxicology study. These evaluations will be conducted by investigators funded by NIEHS. The endpoints were selected based on reports from previous animal toxicology or human epidemiology studies suggesting that they are affected by BPA exposure. Assessments will be conducted at various ages (postnatal days 1, 21, and 90 and 6 and 12 months) and it will be determined if any effects observed are predictive of long-term effects evaluated in the companion chronic toxicology study or reveal potential effects undetected by standard toxicological evaluations.
Neurobehavioral effects of BPA across age and sex *80-05-7* [Ferguson]	(1) To characterize how orally administered BPA or ethinyl estradiol treatment during the perinatal period in Sprague Dawley rats affects anxiety, learning, and memory-related behaviors during juvenile and adult life across three human-relevant dose and one dose of the reference estrogen; and (2) to identify the molecular and morphological changes induced by perinatal BPA treatment or ethinyl estradiol in the hypothalamus and hippocampus, which are critical brain regions governing these behavioral responses.
Assessment of the nephrotoxicity from the 90-day combined exposure to melamine and cyanuric acid in F344 rats *108-78-1, 108-90-5* [Gamboa]	To investigate the nephrotoxic effects noted in F344 rats exposed in NTP study number C10119 to melamine, cyanuric acid and melamine cyanurate. The initial toxicity was reported in the kidneys of the pets and children exposed to adulterated foods.
Assessment of nephrotoxicity from an exposure to melamine, cyanuric acid, and its combination in newborn F344 rats from postnatal day 1 to weaning *108-78-1, 108-90-5* [Gamboa]	(1) To determine if a combined exposure to melamine and cyanuric acid in newborn F344 rats is more nephrotoxic than exposure to the individual compounds, (2) to establish the dose-response curve for the combined exposure, and (3) to investigate the longer-term effects of these lesions during a recovery period.

Study CASRN [Principal Investigator]	Objective and/or Rationale
Two-year carcinogenicity bioassay of furan in Fischer 344 rats *110-00-9* [Beland]	To determine the dose-response relationship for the carcinogenicity of furan in F344/N/NCTR male rats in a two-year bioassay.
Dermal Toxicology Program	
Thirteen-week dermal toxicity of triclosan in B6C3F1 mice *3380-34-5* [Fang]	(1) To determine the toxicity of dermally applied triclosan with ethanol as the vehicle and (2) to determine the possible toxicity and phototoxicity of triclosan under normal use conditions.
Nanoscale Material Program	
Thirteen-week study to evaluate the toxicology of silver nanoparticles in Sprague Dawley rats *744-22-4* [Boudreau]	To determine if exposure over a 13-week period to nanoscale (10, 70, and 107 nm) silver particles induces toxicity.
Reproductive and Developmental Toxicology Program	
Effect of oxybenzone on fertility and early embryonic development in Sprague Dawley rats (Segment I) *131-57-7* [Inselman]	(1) To examine the reproductive toxicity of oxybenzone in male and female rats and focus specifically on fertility and early embryonic development to implantation, and (2) to compare the results of a typical Segment I, II, and III study design with results from a modified one-generation study proposed by the NTP.
Effect of oxybenzone on embryo/fetal development in Sprague Dawley rats (Segment II) *131-57-7* [Inselman]	To determine the potential developmental toxicity of oxybenzone and to compare the results of a typical Segment I, II, and III study design with results from a modified one-generation study proposed by the NTP.
Effect of oxybenzone on pre and postnatal development in Sprague Dawley rats (Segment III) *131-57-7* [Inselman]	(1) To determine the potential toxicity of oxybenzone on pre and early postnatal development in male and female rats, and (2) to compare the results of a typical Segment I, II, and III study design with results from a modified one-generation study proposed by the NTP.

6. Alternative Methods Development

A. Tox21

In FY 2008, NTP established a high throughput screening initiative, representing a new paradigm in toxicological testing. On Feb. 14, 2008, the "Memorandum of Understanding (MOU), High Throughput Screening, Toxicity Pathway Profiling, and Biological Interpretation of Findings," was signed (see *http://ntp.niehs.nih.gov/go/28213* for information about the MOU). Through this MOU, the NIEHS/NTP formally entered into a partnership with NCGC, now at NCATS; and the EPA National Center for Computational Toxicology within the Office of Research and Development. The MOU was amended in 2010 to include FDA, whose active participation is in recognition of its commitment to developing new methods to evaluate the toxicity of the substances it regulates. This interagency partnership is the basis for the Tox21 program, and makes it possible to pool resources to overcome the resource limitations of a single agency, build on existing expertise, and avoid the need to create a new administrative and support structure.

The Tox21 program was developed in response to the 2007 National Research Council report "Toxicity Testing in the 21st Century: A Vision and a Strategy." A central component of the MOU is exploration of quantitative high throughput screening (qHTS) assays, using phylogenetically lower animal species, such as fish and worms, as well as high throughput, whole-genome, analytical methods to evaluate mechanisms of toxicity. The ultimate goal of Tox21 is to provide the data generated by these new tools to risk assessors for use in protecting human health and the environment.

The goals of Tox21 and the NTP high throughput screening program are the same: prioritization of chemicals for further in-depth toxicological evaluation; identification of mechanisms of action for individual chemicals, as well as chemical classes and structures; and, ultimately, predictive toxicology. The results of this collaborative effort should yield test methods for toxicity determination that are more scientifically and economically efficient, inform adverse outcome pathway analyses, and provide models for risk assessment that are more biologically and mechanistically based than current models. This approach should ultimately reduce or replace animals in regulatory testing, and is anticipated to occur in parallel with an enhancement of the ability to evaluate the large numbers of chemicals that currently lack adequate toxicological evaluation.

Phase I

In Tox21 Phase I, conducted from FY 2006 through FY 2010, a library of 2,870 compounds, provided by NTP and EPA to NCGC, was tested in 140 assays, representing 77 predominately cell-based qHTS assays. These assays broadly evaluated the ability of compounds to induce cytotoxicity, apoptosis, DNA damage, changes in methylation status, mitochondrial toxicity, and upregulation of various stress response pathways, such as antioxidant, hypoxia, and heat shock, in a variety of cell types; or to perturb nuclear receptor signaling in 12 different signaling pathways, including those involving the critically important estrogen and androgen receptors.

Phase II

Based on the knowledge gained from Phase I, a screening approach for Tox21 Phase II was identified that would be used to evaluate the biological effects of a 10,500-substance library (8,307 unique), informally known as the 10K library, with approximately one-third of the total substances assembled by each partner. The compounds cover a wide variety of classifications and include consumer products, food additives, chemicals found in industrial processes, and human and veterinary drugs. A complete list of the compounds is publicly

available at *http://www.epa.gov/ncct/dsstox*. Chemical analyses to determine the identity, purity, and stability of all compounds in the library were initiated in FY 2012 and will continue through FY 2014.

In FY 2011, screening of the 10K library began, as well as screening on a subset of approximately 700 of these compounds in Phase II of the EPA ToxCast Program (*http://www.epa.gov/ncct/toxcast*). The data from all these assays, along with full chemical characterizations and assay protocol details, are being deposited into publicly accessible, relational databases, such as the National Library of Medicine's PubChem (*http://pubchem.ncbi.nlm.nih.gov*), EPA's ACToR (*http://www.epa.gov/ACToR*), and NTP's CEBS (*http://www.niehs.nih.gov/research/resources/databases/cebs*).

The 10K library contains 88 duplicate compounds, which are present on each compound plate, as well as approximately 2,100 compounds, which are present in the library in multiple copies and were obtained from different sources. This compound replication provides a means of evaluating interplate and intraplate variability, as well as cross-assay variability in compound activity, as a monitor of the technical quality of a screen. The emphasis during Phase II is on assays measuring nuclear receptor signaling in agonist and antagonist mode, such as aryl hydrocarbon receptor, androgen receptor (partial and full), estrogen receptor alpha (partial and full), farnesoid x receptor, glucocorticoid receptor (full), liver x receptor, peroxisome proliferator-activated receptor delta and gamma, pregnane x receptor, retinoic acid receptor-related orphan receptor, retinoid x receptor, thyroid receptor, and vitamin D receptor; induction of stress-response pathways, such as antioxidant, DNA damage, heat shock, and hypoxia; and assays measuring specific toxicity endpoints, such as mitochondrial membrane changes, caspase activation, aromatase inhibition, and upregulation of nuclear factor kappa beta, a transcription factor that has an important role in the immune system.

In FY 2013, data from 88 qHTS assays measuring activity in 22 nuclear receptor agonist and antagonist assays, eight stress response pathway assays, and three autofluorescence detection assays were released to the public via PubChem. For the majority of assays, cell viability was assessed using a complementary readout in the same wells as the main readout. In addition to the nuclear receptor and stress response assays, compound biological stability was assessed by screening the 10K library at 0, 2, 4, and 6 months of being maintained in use at room temperature in an assay measuring upregulation of p53.

The Tox21 Phase II screening is being conducted in a new, high-speed, robotics screening facility dedicated at the NCGC in FY 2011. It was built with funds provided by NIEHS/NTP. This robotics facility was used to screen the 10K compound library in triplicate (30,000 compounds per screen). In FY 2011, the differential cytotoxicity response of cells from humans was evaluated by screening 1,089 densely sequenced lymphoblastoid cell lines, representing nine racial groups, against 179 toxic chemicals. This study was designed to measure interindividual differences in sensitivity to environmental toxicants, based on genotype. The resulting data were analyzed and, in a collaboration with NCATS, the University of North Carolina (UNC), and Sage Bionetworks, portions of the data were used to conduct the first ever crowdsourcing challenge of its kind, the NIEHS-NCATS-UNC DREAM Toxicogenetics Challenge (see **page 19** for more details about the challenge).

Table 29 describes the NTP Tox21 projects in FY 2013 that are being carried out by NIEHS/NTP staff. This includes projects in the NTP WormTox Facility, which develops toxicological assays using the nematode *Caenorhabditis elegans (C. elegans)*, and evaluates their utility as medium throughput screening tools. The use of *C. elegans* is consistent with the NTP strategy to reduce the number of mammals used in testing. In FY 2012, screening using the *C. elegans* growth assay was completed on the EPA ToxCast Phase II chemical library of 700 compounds. The data from this screen have been analyzed, and a manuscript describing the results is in the process of completion.

Table 29. NTP Tox21 Projects in FY 2013	
NTP Project Title [Study Scientist]	**Objective and/or Summary**
Assay Development	
Developing a stable cell line to screen compounds that effect the estrogen-related receptor/ peroxisome proliferator-activated receptor coactivator pathway [Merrick]	To develop an assay that would detect compounds that interfere with the estrogen-related receptor/peroxisome proliferator-activated receptor gamma coactivator pathway, a critical pathway for metabolic homeostasis. Two steps are required to develop the stable cell line and the first step to produce stable cell lines expressing peroxisome proliferator-activated receptor gamma coactivator-1-alpha has been accomplished, with an expectation that the assay will be functional in late FY 2014.
High content screening with HepaRG cells [Ferguson]	To establish metabolically functional human HepaRG liver cells in 96- or 384-well format to multiplex high content screening assays in collaboration with the NCGC.
Testing for gene signatures and profiles in NTP archival tissues project [Merrick]	To determine if RNA can be extracted from fixed tissue blocks in the NTP Archives in order to measure gene signatures and develop chemically-induced transcriptomics profiles. The potential usefulness of the NTP Archives is for measuring molecular changes in different organs of the rat and mouse caused by chemical exposures.
Stem cells projects [Ferguson]	To screen for chemical toxicity in human or mouse stem cell lines (undifferentiated or differentiated) by qHTS at the NCGC or using lower throughput assays at NIEHS. Initially, the project is focused on fostering collaborations with stem cell technology providers and assessing control compounds and subsets of NTP chemicals using various assay approaches. Stem cell technology platforms and model systems shown to be useful for in vitro toxicology screening would be employed with larger sets of chemicals for hazard identification and chemical prioritization for toxicity testing.
Assay Interpretation	
Validation of high throughput screening estrogen receptor (ER) qHTS transactivation assay [Casey]	(1) To compare the quality and accuracy of the qHTS assay that evaluates transcriptional activation of the ER in human ovarian cancer cells (BG1 ER transactivation assay (TA) assay) relative to the manual method that has been validated for regulatory use (EPA and Organisation for Economic Co-operation and Develop). The results of this evaluation indicate that the performance of the high throughput screening method is equivalent to the manual method. A manuscript detailing these results will be published in 2014. (2) To compare the BG1 ER TA assay (full-length receptor) with the assay that evaluates transcriptional activation of the estrogen receptor in human embryonal kidney cells (HeK293 ER TA assay) that uses a transfected partial (ligand binding domain) receptor. Reproducible qHTS data were obtained in both assays, but there are differences in the percentages of compounds classified as active and negative. Understanding the factors contributing to differences in performance of these assays is critical to their regulatory acceptance and utilization. Once the quality of the data is deemed to be sufficient (anticipated to occur in FY 2014), results can be used to assess and further develop quantitative structure-activity relationship models for ER binding.
Data Analysis	
Modeling mixtures of androgen receptor- and estrogen receptor-active compounds screened in Tox21 qHTS assays [Parham]	To determine (1) which mathematical models can best describe the toxicity of the mixtures of these compounds and (2) whether the behavior of the mixtures can be predicted from the behavior of the individual components. (3) Collaborative work with the University of North Carolina at Chapel Hill involves providing data for their structure-activity relationship mixture model.

NTP Project Title [Study Scientist]	Objective and/or Summary
Analysis of Tox21 qHTS assay data [Hsieh]	To develop data analysis pipelines for Tox21 Phase II qHTS data to determine the activity of compounds in assays. The developed ranking/calling procedure takes into account compound potency, efficacy, and data reproducibility. A publication describing this pipeline is expected to be published in FY 2014.
Prioritization of Tox21 compounds for genotoxicity [Hsieh]	To develop a prioritization approach that not only includes compounds that show clear evidence of activity in the qHTS genotoxic assays, but also weakly active compounds based on chemical structure-activity relationship analysis.
Design of Tox21 data exploration graphical user interface [Hsieh]	To develop two graphical user interfaces for viewing Tox21 data. One graphical user interface is to explore the concentration-response data in a line chart, the second graphical user interface is to explore compound-similarity relationships in terms of their activities in Tox21 qHTS assays and their chemical structures. Prototype graphical user interfaces were developed during FY 2013 with general usage scheduled for FY 2014.
Low-dose extrapolation for Tox21 Phase I qHTS data [Parham]	To determine points of departure for low-dose extrapolation by using signal-to-noise ratios and a benchmark-dose method.
Sequencing quality control toxicogenomics project [Auerbach]	To compare transcriptomic technologies (technologies that examine the RNA molecules in a cell population by microarray, high throughput screening, etc.) within the context of toxicogenomics. This is a multi-organization, international collaboration.
Genomic signatures forecasting chemical carcinogenicity project [Auerbach]	To develop transcriptomic signatures related to carcinogen treatment using NTP's DrugMatrix data in combination with a machine-learning approach. Signatures are being validated using an independent set of data from the Japanese Toxicogenomics Project.
Unsupervised, data-driven analysis of Tox21 assay data project [Auerbach]	To employ unsupervised data analysis (data organization based on patterns and performed by software) methods to identify chemicals that exhibit similar biological properties to well characterized toxicants among the qHTS assays used to screen the 10K library.
Next generation sequencing in toxicology project [Merrick]	To develop pipelines for genomic and transcriptomic gene expression and mutational analysis on a genome-wide level using next generation sequencing technologies to build signatures of toxicity and chemical exposure.
Development of a database related to skin sensitization [Casey]	To develop the world's largest public database for skin sensitization. This database, which is publically available on the NICEATM website, serves as a valuable resource for reference data to help develop alternative toxicological methods, including quantitative structure-activity relationship models that can be used to eliminate the use of animals. Such data are useful for evaluating in vitro results obtained in the Tox21 program. Collaborations with the EPA to evaluate submitted studies and expand the database even further are underway.
In silico prediction of metabolism project [Ferguson]	To evaluate various in silico methods of predicting the extent of xenobiotic metabolism, identity metabolites and prioritize chemicals in the Tox21 10K library. Computational methods will be used to 'bin' the 10K library and develop sub-sets of chemicals likely to be appreciably metabolized in humans.
Selection of a target set of genes for use in a high throughput transcriptomics screen [Paules]	(1) To identify patterns of exposure-induced biological responses in order to characterize toxicity and disease pathways and (2) to facilitate extrapolation of findings from model species to humans. To accomplish this, an effort has been initiated to select a set of genes (~1,000 to 1,500) to best capture and represent the full biological response to exposures and disease to be utilized in a high throughput transcriptomics screen. Criteria are being developed for the selection of the best target set of genes for this purpose. Efforts included a workshop in September 2013 to examine the utility and feasibility identifying such a targeted set of genes for humans, rats, mouse, zebrafish, and *C. elegans*. Expectations are that a draft human list will be released by mid FY 2014 for comment by the scientific community.

NTP Project Title [Study Scientist]	Objective and/or Summary
Testing Projects	
Epigenetic changes in chemical toxicity project [Merrick]	To determine methylation patterns on a genome-wide basis and validation of selected CpG sites (regions of DNA where a cytosine nucleotide occurs next to a guanine nucleotide) altered by chemical exposure. Methylation of CpG sites can turn a gene off while demethylation can cause transcriptional activation.
Screening for aromatase inhibitors in the Tox21 10K library [Merrick]	To screen aromatase inhibitors in the Tox21 10K library, collaboration was established with Dr. Shiuan Chen at Beckman Institute, City of Hope, CA to develop an "AroER Tri-screen." The 10K library was screened in this assay and the resulting data are being analyzed.
Polycyclic aromatic hydrocarbon (PAH) project [Ferguson]	To evaluate approximately 20 PAHs considered relevant to human exposure in metabolism-competent HepaRG cells (derived from a human hepatic progenitor cell line) using multiplexed high-content screening assays and gene expression platforms.
Analysis of NTP's 52 compounds in EPA's ToxCast Phase II program [Casey]	To screen 52 compounds in the EPA's ToxCast program based largely on immunological relevance. NICEATM will use in vitro chemical profiling data to identify predictive signatures and adverse outcome pathways anchored to in vivo endpoints and toxicity pathways. These analyses will be used to enable chemical prioritization and hazard predictions. Preliminary analyses have been conducted, and compounds and assay systems for potential targeted testing have been identified.
NTP WormTox Laboratory Projects	
Assay development [Boyd]	To develop reproduction, growth, feeding, and locomotion assays that measure the effects of toxicant exposure on complex biological phenotypes including development and neuron function. These assays have been developed in addition to an inducible gene expression fluorescence assay in transgenic *C. elegans* that measures stress pathway activation using high-content imaging system. Two mitochondrial toxicity assays are in development: (1) an in vivo adenosine-5'-triphosphate assay, which provides real-time energetic status of the nematode, and (2) a fluorescence dye-based mitochondrial membrane potential assay. Additionally, a low-throughput *C. elegans* mitochondrial DNA damage and repair assay has been developed.
EPA's ToxCast Phase II project [Boyd]	(1) To determine the effects of the EPA's ToxCast Phase II 700-compound library on *C. elegans* development and (2) to compare the relative toxicities to those in higher organisms. The in vivo studies were completed in FY 2013 and data analysis is scheduled for completion in FY 2014.
Ionic liquids project [Boyd]	(1) To describe the effects of ~200 ionic liquids on *C. elegans* feeding, growth, and reproduction and (2) to compare the results in *C. elegans* to results in rodents and other toxicological models.
Flame retardants project [Boyd]	(1) To describe the effects of eight flame retardants on *C. elegans* feeding, growth, and reproduction and (2) to compare the results in *C. elegans* to results in rodents.
Mitochondrial toxicants project [Boyd]	To determine the effects of the mitochondrial toxicant subset from the Tox21 10K library on *C. elegans* growth and in vivo adenosine-5'-triphosphate levels and membrane potential.
Fluorides project [Boyd]	To compare the toxicities of three fluoride compounds commonly used in drinking water treatment processes on *C. elegans* feeding, growth, and reproduction. The in vivo studies have been completed and the resulting manuscript was accepted for publication.

B. ICCVAM

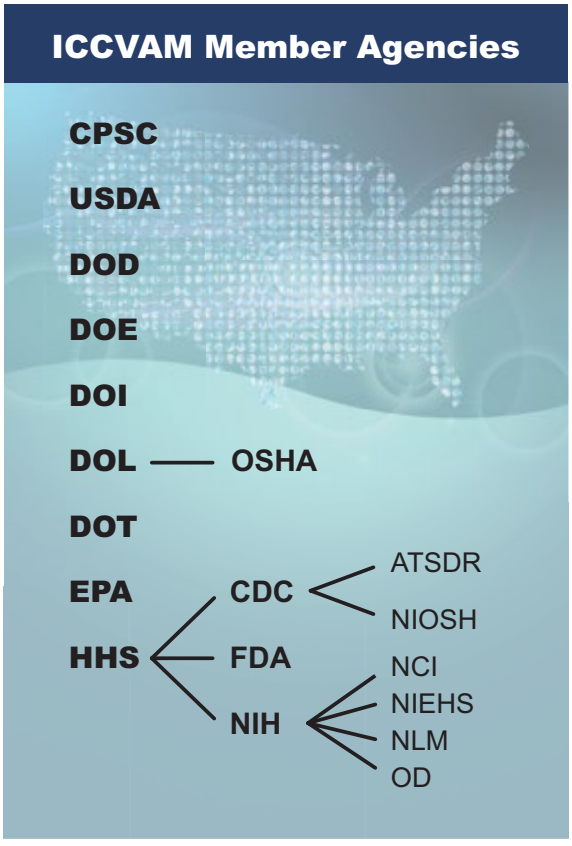
The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) is composed of representatives from 15 U.S. federal regulatory and research agencies that generate or use toxicological and safety testing information. The purpose of ICCVAM is to promote the regulatory acceptance of scientifically valid new test methods that replace, reduce, or refine animal use.

NICEATM administers ICCVAM and provides scientific support for ICCVAM activities. In addition to its support of ICCVAM, NICEATM:

- Supports NIEHS/NTP activities, especially those related to Tox21.
- Conducts analyses and evaluations, and coordinates independent validation studies on promising test methods.
- Provides information to test method developers, regulators, and regulated industry, through its website and workshops on topics of interest.

In FY 2013, the NICEATM website was integrated into the NTP website. Information on NICEATM activities is located at *http://ntp.niehs.nih.gov/go/niceatm*. The new NICEATM website includes resources for test method developers at *http://ntp.niehs.nih.gov/go/resources*. Information on ICCVAM activities is available on the NTP website at *http://ntp.niehs.nih.gov/go/iccvam*.

Upon the retirement of Rear Adm. William Stokes in December 2012, Warren Casey, Ph.D., became acting director of NICEATM for the remainder of FY 2013. Casey also served as administrative director of ICCVAM. NICEATM received contract support during FY 2013 from Integrated Laboratory Systems Inc.



i. Workshops

NICEATM worked with ICCVAM member agencies and international partners to organize the International Workshop on Alternatives to the Murine Histamine Sensitization Test (HIST) for Acellular Pertussis Vaccines. The workshop was held Nov. 28–29, 2012, at the William H. Natcher Conference Center at NIH in Bethesda, Maryland. Workshop participants reviewed and discussed data generated by an international study that compared the performance of 12 in vitro assays. Two cell-based assays that appeared most promising for future acceptance or adoption were recommended for further development and optimization. Workshop participants supported development of a standardized Chinese hamster ovary cell aggregation assay as an alternative to the murine histamine sensitization test for calibration of pertussis toxin reference standards. The workshop report is in press in Biologicals and will be published in early 2014. Links to the workshop report, summary, presentations, and other information are at *http://ntp.niehs.nih.gov/go/HISTwksp*. Follow-up workshops are planned for August 2014 and mid-2015.

ii. Publications

The following FY 2013 publications describe NICEATM and ICCVAM activities.

Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). 2012. ICCVAM Test Method Evaluation Report: Identifying Chemical Eye Hazards with Fewer Animals. NIH Publication No. 12-7930. Research Triangle Park, N.C.: National Institute of Environmental Health Sciences.

Johnson N, Doelling V, Jones B, eds. 2013. International Workshop on Alternative Methods for Vaccine Potency Testing: State of the Science and the Way Forward. Biologicals 41(5):279–338.

Kolle SN, Basketter DA, Casati S, Stokes WS, Strickland J, van Ravenzwaay B, Vohr HW, Landsiedel R. 2013. Performance standards and alternative assays: practical insights from skin sensitization. Regul Toxicol Pharmacol 65(2):278–285.

A complete list of articles on NICEATM and ICCVAM activities published in scientific journals is available at *http://ntp.niehs.nih.gov/go/niceatm-pubs*. Reports published by NICEATM are available at *http://ntp.niehs.nih.gov/?objectid=E2E87900-F051-C3CA-C6C4A81E33A38907*.

iii. NICEATM Activities

NICEATM Support of Tox21

Following a NICEATM nomination, the estrogen receptor (ER) transactivation (TA) test method was adapted to a high throughput format by NCATS and used to screen the Tox21 10K chemical library. NICEATM analyzed the results and determined that the high throughput BG1Luc ER TA test method performed well when compared against the validated manual method.

NICEATM also compared data from the BG1Luc ER TA test method to an ER beta-lactamase method, which was already being used in the Tox21 program. The ER beta-lactamase method differs from the BG1Luc ER TA method in that the cell line used includes a partial ER receptor that contains only the ligand binding site of the ER. Results from the BG1Luc ER TA and ER beta-lactamase were compared both to each other and to reference data. The study found that the two methods produced data of acceptable quality and results that agreed mostly, but not completely, with each other and with the reference data. Understanding the factors contributing to differences in performance of these assays is critical to their regulatory acceptance and utilization.

Other NICEATM Activities

NICEATM is collecting oral and dermal toxicity data to evaluate if acute oral toxicity data could be reliably used to assign EPA acute dermal hazard classifications, potentially reducing the number of animals needed for pesticide testing. EPA is providing NICEATM with acute oral toxicity data for both pesticide-active ingredients and pesticide formulations. NICEATM is reviewing the data for quality control purposes and using modified Klimisch criteria to evaluate the reliability of the data.

Scientists within NICEATM and NIEHS are collaborating with scientists at Procter and Gamble to develop an approach that can identify potential skin sensitizers and characterize skin sensitization potency, without conducting animal tests. The goal of the collaboration is to develop a widely available, opensource version of an integrated testing strategy developed by Procter and Gamble. The open-source integrated testing strategy will be described in a short communication in the journal ALTEX in 2014. Downloadable files to run the analysis, along with documentation and sample data, are available at *http://ntp.niehs.nih.gov/go/its*.

NICEATM scientists worked with immunotoxicologists from NIEHS/NTP, EPA, and other academic institutions and international organizations, to create a standardized ontology for in vivo immunotoxicity data. Using the standardized ontology, NICEATM is working with EPA to create a comprehensive database consisting of high-quality data from in vivo testing of potential immunotoxicants. This database will support the validation of high throughput, in vitro test methods for prediction of allergic contact dermatitis and other immunotoxic effects.

NICEATM is creating a comprehensive database of highquality, in vivo testing data from 52 chemicals selected by EPA and NIEHS/NTP, to support future validation of high throughput, in vitro test methods and in silico models of estrogenic activity. Studies selected included data for a number of different endpoints that indicate estrogenic activity. Information from references is being extracted and compiled using a standardized ontology. A semiautomated, graphical user interface is being developed to evaluate the quality of the data in an efficient and standardized manner, according to modified Klimisch criteria (Schneider et al. 2009. "ToxRTool," a new tool to assess the reliability of toxicological data. Toxicol Lett 189(2),138–144). The NICEATM database will be made available on the NTP website at *http://ntp.niehs.nih.gov/go/40658*.

NICEATM activities initiated in FY 2013 to support risk-based, chemical testing prioritization include construction of reverse toxicokinetic models to assist in vitro to in vivo extrapolation, and development of approaches to estimate bioconcentration potential and exposure.

iv. Test Method Evaluation Activities

ICCVAM received no formal test method nominations or submissions in FY 2013. ICCVAM is currently revising its test method evaluation procedures, of which nominations and submissions are a key element. ICCVAM welcomes submissions of innovative test methods that may be acceptable for specific regulatory use, and for which adequate validation studies have been completed. However, to maximize the potential for effective implementation of new test methods or approaches, ICCVAM will only conduct evaluations and prepare recommendations on test method submissions proposed for regulatory uses that align with ICCVAM member agency needs and priorities. More information on ICCVAM test method submissions is available at *http://ntp.niehs.nih.gov/go/ICCVAM-submit*. NICEATM and ICCVAM test method evaluation activities in FY 2013 are summarized in **Table 30**.

Table 30. Test Method Evaluation Activities in FY 2013

Test Method	ICCVAM Recommendations/Agency Status
OptiSafe test for identifying potential eye irritants	NICEATM evaluated the validation study data for OptiSafe, an in vitro test method for identification of potential eye irritants. Initial review of the data indicates that the OptiSafe method may compare favorably to other in vitro eye-safety testing methods. ICCVAM will reactivate its Ocular Toxicity Working Group to more thoroughly evaluate this test method to determine its potential regulatory utility and whether additional activities are necessary.
ICCVAM plan for the evaluation of alternative skin-sensitization test methods and testing strategies	ICCVAM is developing a plan for the evaluation of alternative, skin-sensitization test methods and testing strategies. Proposed activities include collaboration with international partners to support ongoing development and validation of in vitro skin-sensitization test methods, evaluation of alternative test method and testing strategy submissions, and promotion of validated methods through workshops, webinars, and guidance documents. The newly established ICCVAM Skin Sensitization Working Group is considering comments received on this proposal and will advance recommendations for appropriate ICCVAM activities for the next several years. More information is available at *http://ntp.niehs.nih.gov/go/40498*.

v. International Validation Activities

NICEATM and ICCVAM participate in international, test method validation activities through the Organisation for Economic Co-operation and Development (OECD) and collaborations with countries that are members of the International Cooperation on Alternative Test Methods (ICATM). In FY 2013, NICEATM and ICCVAM were involved in the following OECD activities:

- Incorporation of ICCVAM performance standards into 2013 updates of OECD test guidelines describing in vitro methods to identify potential dermal corrosives.
- A presentation by Casey, representing NICEATM and ICCVAM, at the November 2012 Validation Management Group for Non-Animal Testing meeting, part of the OECD Task Force on Endocrine Disrupters Testing and Assessment.
- Participation of Casey at the November 2012 meeting of the OECD Thyroid Scoping Effort Expert Group. This meeting initiated an effort to identify available assays for the detection of potential thyroid disruptors, and assess their suitability for regulatory use or potential future test guideline development. As a follow-up activity, NICEATM staff collected information on available thyroid assays and submitted it to the group for inclusion in a larger report that will be reviewed by OECD in 2014.

Ongoing international validation studies that include participation of NICEATM or ICCVAM are listed in **Table 31**. Casey represented NICEATM and ICCVAM at an ICATM coordination meeting in February 2013.

Table 31. Participation in International Validation Studies

Test Method	Type of Test	Lead Organization	NICEATM-ICCVAM Involvement
EpiOcular (MatTek) and SkinEthic (L'Oreal)	Ocular irritation	EURL ECVAM	NICEATM and ICCVAM members served on the validation management team and provided comments on study design, chemical selection, and test method performance criteria.
Human cryopreserved HepaRG and cryopreserved hepatocytes cytochrome p450 induction test methods	Acute toxicity	EURL ECVAM	NICEATM and ICCVAM members served on the validation management team and provided comments on study design, chemical selection, test method protocols, and study reports.
In vitro tests for assessing skin sensitization potential of chemicals	Allergic contact dermatitis	EURL ECVAM	NICEATM and ICCVAM members served on the validation management team and provided comments on study design, chemical selection, and test method protocols.
In vitro tests for assessing skin sensitization potential of chemicals	Allergic contact dermatitis	JaCVAM	NICEATM and ICCVAM members served on the validation management team and provided comments on study design, chemical selection, and test method protocols.
Short-time-exposure test for identifying potential eye irritants	Ocular irritation	JaCVAM	NICEATM prepared a summary review document that presents an evaluation of short-time-exposure test-method performance based on test substances with corresponding in vivo data (*http://ntp.niehs.nih.gov/iccvam/docs/ocutox_docs/STE-SRD-NICEATM-508.pdf*). The evaluation underwent an independent peer review coordinated by NTP. The reviewers made a number of comments with respect to the usefulness and limitations of the short-time-exposure method for consideration by regulatory agencies when such data are submitted.

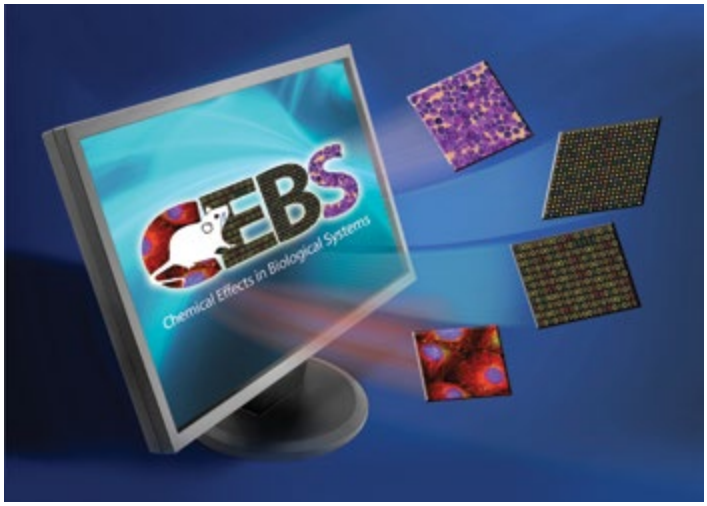
7. Public Tools

NTP provides a variety of resources for public use. Those available in FY 2013 are described below.

A. Nonneoplastic Lesion Atlas

NTP Nonneoplastic Lesion Atlas is a web-based resource containing hundreds, and eventually thousands, of high-quality images and guidelines for nonneoplastic lesions in experimental rodent models. The purpose of the atlas is to standardize the terminology, diagnostic strategy, and record of nonneoplastic rodent lesions, to improve the consistency of the NTP nonneoplastic lesion database. The atlas is planned for launch in FY 2014. See **page 17** for more information about the atlas.

B. Chemical Effects in Biological Systems (CEBS) Database



CEBS is a publicly accessible, NTP-integrated data-management system that houses biological study data deemed of interest to toxicologists and environmental health scientists. The CEBS database was designed as a reference repository, and accepts studies from many sources. Government, academic, and pharmaceutical laboratories contribute peer-reviewed studies to the database.

An important feature of the database is its flexibility. CEBS can house any type of biological measurements from any type of study design. This flexibility allows data from different sources to be integrated into one place, to permit data mining and analysis. In addition, any one study can have different types of data associated with it, such as blood chemistry, histopathology, and microarray, and can all be viewed together by one study name.

NIEHS continues to add legacy NTP data to CEBS. Phase II Tox21 data will also be publicly available through CEBS, as the studies are released for reference and data mining. CEBS supports queries such as “show me all test articles that cause a particular pathology” or “show me all test articles positive in a particular genetic toxicology assay,” where “test articles” is the database term used to refer to substances being tested, such as chemicals or drugs.

CEBS captures the details of a study’s design and execution, as well as the biological responses of study subjects, such as animals and tissue culture cells. This enables the user to view the details of each study; search for particular studies or study subjects of interest, based on treatment, response, or other characteristics; and then either analyze the data within CEBS or download for import into other tools. CEBS can be accessed at *http://cebs.niehs.nih.gov*.

C. NTP Archives

The NTP Archives is an important NIEHS-supported resource that houses an unmatched collection of research specimens and supporting data from more than 2,000 studies, including toxicity, carcinogenicity, immunotoxicity, reproductive, and developmental studies. Currently, the NTP Archives maintains 7.7 million histopathology slides, 4.8 million paraffin-embedded tissue blocks, 213,000 bags of formalin-fixed tissues and organs, 117,000 selected frozen tissue specimens; and study data including 4.4 million pages of paper records, 10.8 million pages of data on microfiche, and 2.4 million pages of digital or electronic records on CDs or DVDs. It also houses histological images, including more than 38,000 kodachrome slides and 27,000 digital images, in a publically accessible, searchable, Web-based database, as well as educational and training materials on rodent toxicologic pathology on CDs and DVDs.

The NTP Archives provides researchers unique opportunities to characterize and compare diverse disease or disease processes that occur spontaneously or are chemically induced, examine collections of rare and unusual lesions, and explore observed pathologic responses at the cellular or molecular level to determine mechanisms of disease. There are ongoing efforts to organize the archives, to make it more electronically searchable for chemical exposure related to toxicity phenotype at the animal level and to recommend protocols consistent with best practices for biobanking and archival storage. There are also ongoing efforts to determine the usefulness of archival materials for various types of molecular analysis, including gene expression, epigenetics, and mutational analysis.

A recent gene expression study, using archival material, showed that a gene expression signature, comprised of 14 different transcripts, could be reliably measured from RNA extracted from four-year-old, formalin-fixed, paraffin-embedded (FFPE) liver tissues in an NTP 90-day rat study. FFPE RNA from liver, kidney, and lung, to a lesser extent, were of sufficient quality for molecular analysis to measure gene expression by quantitative polymerase chain reaction that favorably compared to results of fresh frozen tissues from identical animals. These studies demonstrated the usefulness of archival tissue blocks for gene profiling. A more systematic query of archival materials, from different organs and storage times, is planned for the future, to more precisely determine the value in transcript profiling of the NTP Archives.

More information about the archives can be found at *http://ntp.niehs.nih.gov/ntp/pressctr/brochures/ntparchives2014_508.pdf*.

D. The NCGC BioPlanet

No single, comprehensive, uniform resource covers all known annotations of cellular pathways, and no single platform allows integrated browsing, retrieval, and analysis of information from the many existing resources that do pathway mapping. Therefore, NCGC, with support from NIEHS through NTP (see **page 16**), built an integrated pathway resource that hosts information on approximately 1,600 human pathways from manually curated and publicly available resources. The NCGC BioPlanet complements this pathway warehouse, by allowing easy browsing, visualization, and analysis of the universe of pathways. The BioPlanet is scheduled for public release in 2014.

E. DrugMatrix and ToxFX

Related to the goal of developing analysis tools and approaches, to allow an integrated assessment of high throughput screening endpoints and associations with findings from traditional toxicology and cancer models, NTP acquired DrugMatrix, a toxicogenomics reference database, as well as the accompanying extensive

frozen tissue archives and informatics system. This resource expands the ability of NTP to develop predictive models for toxicological effects based on gene signatures, provide additional tools for linking in vitro data to in vivo gene signatures and disease outcomes, and provide additional tissue samples for NextGen-based investigations. DrugMatrix and its companion automated analysis tool ToxFX were made accessible to the international scientific community in early FY 2012 (*https://ntp.niehs.nih.gov/drugmatrix* and *https://ntp.niehs.nih.gov/toxfx*). To date, more than 475 researchers have registered to use the DrugMatrix database. In addition, the data and biological samples from DrugMatrix are a focal point in a number collaborations between NIEHS/NTP scientists and research groups from NCTR, the City of Hope, Stanford University, Boston University, EPA, Health Canada, Abbott Laboratories, Eli Lilly and Company, SAS, Maastricht University, GeneData, University of Massachusetts, and University of North Dakota. Samples from the DrugMatrix frozen tissue bank have been analyzed through the MicroArray Quality Control/Sequencing Quality Control Consortium (*http://www.fda.gov/ScienceResearch/BioinformaticsTools/MicroarrayQualityControlProject/default.htm*) in collaboration with researchers at Harvard University. Finally, all the RNA expression, such as transcriptomics, data from DrugMatrix has been integrated in NextBio, a database and analysis tool, allowing analysis of the data within the context of all existing genomic and transcriptomic data. All DrugMatrix data have been made available through an easily accessible FTP portal (*ftp://anonftp.niehs.nih.gov/drugmatrix*). Ultimately, the goal of these collaborations and data sharing is to use the DrugMatrix data to better understand the molecular underpinnings of disease and toxicological pathology.

F. Meta Data Viewer

Staff within the Office of Health Assessment and Translation developed Meta Data Viewer, in collaboration with SRA International, to be a user-friendly program for creating figures with multiple columns of accompanying text, such as forest plots of epidemiology data or exposure-response arrays of toxicology data. The program allows users to quickly sort, group, and filter subsets of data from a larger database, to look at patterns of findings across a wide variety of studies or sets of results from a single study. Meta Data Viewer is a public resource. Users are welcome to use the program and any associated NTP data files for their own purposes, including use in publications. Meta Data Viewer is available at *http://ntp.niehs.nih.gov/go/tools_metadataviewer*.

8. Appendices

A. Program Contact Information

National Toxicology Program: ***http://ntp.niehs.nih.gov***

General Inquiries: NIEHS/NTP Central Data Management Office; CDM@niehs.nih.gov, 919-541-3419

General Comments: Office of Liaison, Policy and Review, NIEHS/NTP; ntpinfo@niehs.nih.gov, 919-541-7539

NIEHS main website: *http://www.niehs.nih.gov*

NCTR main website: *http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/default.htm*

NIOSH main website: *http://www.cdc.gov/niosh*

Staff directory: *http://directory.psc.gov/employee.htm*

B. Frequently Used Abbreviations

3TC	lamivudine
ADME	absorption, distribution, metabolism, and excretion
ATSDR	Agency for Toxic Substances and Disease Registry
AZT	3'-azido-3'-deoxythymidine
BPA	bisphenol A
BSC	Board of Scientific Counselors
CASRN	Chemical Abstracts Service Registry Number
CDC	Centers for Disease Control and Prevention
CDMA	code division multiple access
CEBS	Chemical Effects in Biological Systems
CLARITY-BPA	Consortium Linking Academic and Regulatory Insights on BPA Toxicity
CPSC	U.S. Consumer Product Safety Commission
DOD	Department of Defense
DOE	Department of Energy
DOI	Department of the Interior
DOL	Department of Labor
DOT	Department of Transportation
ECVAM	European Centre for the Validation of Alternative Methods
EPA	Environmental Protection Agency
ER	estrogen receptor
FDA	U.S. Food and Drug Administration
FFPE	formalin fixed, paraffin embedded

FY	fiscal year
GABA	gamma-amino butyric acid
GD	gestational day
GMM	genetically modified model
GSM	global system for mobile communication
HHS	U.S. Department of Health and Human Services
HIST	murine histamine sensitization test
IARC	International Agency for Research on Cancer
ICATM	International Cooperation on Alternative Test Methods
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
IgE	immunoglobulin E
JaCVAM	Japanese Center for the Validation of Alternative Methods
KoCVAM	Korean Center for the Validation of Alternative Methods
LC/ESI/MS/MS	liquid chromatography-electrospray ionization/multi-stage mass spectrometry
LIFE	Longitudinal Investigation of Fertility and the Environment
MOU	Memorandum of Understanding
N/A	not applicable
NCATS	National Center for Advancing Translational Sciences
NCEH	National Center for Environmental Health
NCGC	NIH Chemical Genomics Center
NCI	National Cancer Institute
NCTR	National Center for Toxicological Research
NICEATM	NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
NFV	nelfinavir mesylate
NHGRI	National Human Genome Research Institute
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
NTP	National Toxicology Program
NVP	nevirapine
OD	Office of the Director, NIH
OECD	Organisation for Economic Co-operation and Development
OHAT	Office of Health Assessment and Translation
OSHA	Occupational Safety and Health Administration
PAC	polycyclic aromatic compounds
PCB	polychlorinated biphenyl
PCBTF	chloro-4-(trifluoromethyl) benzene

Pig-A	phosphatidylinositol glycan complementation group A
PND	postnatal day
qHTS	quantitative high throughput screening
RoC	Report on Carcinogens
SACATM	Scientific Advisory Committee on Alternative Toxicological Methods
SOT	Society of Toxicology
TA	transactivation
TOX	NTP Toxicity Report
TR	NTP Technical Report
UNC	University of North Carolina
U.S.	United States
USDA	U.S. Department of Agriculture
VOC	volatile organic compound

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National Toxicology Program
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